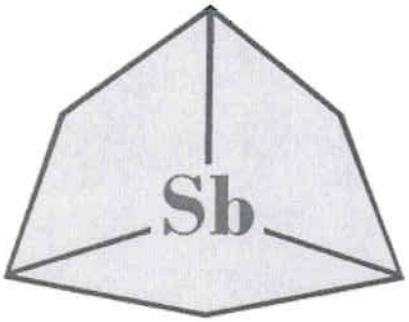


International
ANTIMONY
OXIDE
Industry Association

April 18, 2006

Rec'd 5/10/06

Dr. Scott A. Masten
Office of Chemical Nomination and Selection, NIEHS/NTP
111 T.W. Alexander Dr
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Nomination of Antimony Trioxide for Chronic Testing by NTP/ Testing Recommendations. Response to Federal Register Notice of April 11, 2006.

Dear Dr. Masten,

This letter is submitted on behalf of the industry consortium, International Antimony Oxide Industry Association (IAOIA) in response to the nomination of antimony trioxide (ATO) [CAS No.: 1309-64-4] for chronic and carcinogenicity toxicology as well as cardiotoxicology testing by the NTP. More specifically, we would like to respond to the recent Federal Register Notice of April 11, 2006 Vol. 71, No. 69. In this notice the NTP Office of Chemical Nomination and Selection announces a "Request for comment on Toxicological Study Nominations to the NTP" and further indicates that the Study Recommendations in Table 1 will be discussed at a public meeting on June 13, 2006.

The IAOIA is in support of the proposal to conduct appropriate long-term chronic and carcinogenicity studies in rodents. We understand the basis for the original nomination was a concern over the high number of individuals who are occupationally exposed to this material. It was also inferred from the original nomination that the route of exposure would be by inhalation as this is the primary route of concern in the workplace. While we do not believe that workers are at risk for developing lung tumors as a result of occupational exposures at the current Threshold Limit Value (TLV) of 0.5 $mg/m^3$, we do believe that a chronic study conducted under current guidelines is needed to better understand the carcinogenic potential of ATO.

Furthermore, in the recent FR notice referenced above, the U.S. Consumer Product Safety Commission (CPSC) has suggested that ATO should be studied based on an "Anticipated increased use in upholstered furniture bedding and potential consumer exposures from these uses; insufficient toxicity data to assess potential health risks." The CPSC staff in their letter to the NTP dated August 1, 2005 recommended 1) Chronic oral studies in rats and/or mice and 2) chronic inhalation study in a second species, such as hamster. Furthermore it is suggested that nanoscale materials, if used in the flame retardant process for textiles and bedding applications, should also be assessed. The CPSC stated that exposures to ATO via dermal, inhalation, and oral routes are possible during manufacture

and from downstream uses of flame-retardant materials consumer applications such as automobile interiors, infant sleepwear, and home furnishings. The IAOIA concurs with this assessment and also supports the ongoing CPSC assessments for safe use of selected flame retardants and the development of a performance standard to reduce the potential for ignition of upholstered furniture by cigarettes and small open flames, such as matches, cigarette lighters, and candles. The IAOIA also believes that several hundred deaths, thousands of injuries, and millions of dollars in property loss could be avoided by the implementation of such a standard. Further to this end, the IAOIA believes that ATO, as an important flame retardant synergist can be used safely as evidenced by the toxicology database already available on ATO.

Accordingly, the IAOIA would like to stress that chronic inhalation studies are needed to resolve contradictions present in the current carcinogenicity database. As noted in our original summary of the existing ATO dataset, and the summary prepared by the NTP, there is a need to resolve the limitations and inconsistencies present with respect to the appearance of lung tumors in female rats and absence of tumors in males. For completeness, included below is our original comment of June 1, 2005:

> As mentioned in the basis for nomination, the database on antimony (Sb) compounds is limited to three inhalation studies in rats exposed to ATO particles for one-year duration . The most recently completed study by Newton *et al.1994* was conducted by the Antimony Oxide Industry Association (AOIA). This study consisted of a one-year exposure period followed by a one-year recovery period. The protocol for this study was agreed between the U.S. EPA and the AOIA pursuant to the request from EPA and the subsequent sanctioning of this protocol by the U.S. EPA through the Negotiated Testing Agreement process. This study was conducted using modern testing equipment and methods, and was in compliance with Good Laboratory Practice (GLP) standards. In this study the highest exposure concentration of 4.5 $mg/m^3$ resulted in impaired clearance rates but did not result in an increased incidence of tumors in the lungs of either male or female rats compared to controls. The IAOIA would like to note that even though ATO exposures ceased at 12 months, the animals were kept and observed for another 12 months prior to their termination with still significant levels of ATO dust remaining in the lungs as ATO is very insoluble.
>
> As pointed out in the basis for nomination, this study was not considered by the International Agency for Research on Cancer (IARC) when they concluded antimony trioxide should be classified as a group 2B, *possibly carcinogenic to humans*. There are two studies which were considered by IARC demonstrating the appearance of tumors in the lungs of rats. Again both these studies only exposed animals to ATO for 12 months followed by terminal sacrifices after a recovery period of either 5 (Groth *et al 1986.*) or 12-15 months (Watt 1983). In the studies conducted by Groth *et al 1986.*, animals were exposed to both ATO and an Sb-ore there was a tumor incidence rate of 27% (ATO) or 25% (Sb-ore) in females only (no tumors were seen in males) without regard to whether they were exposed to antimony as ATO (45.5 $mg/m^3$, 80% Sb ug/g) or as an antimony ore (38 $mg/m^3$, 46% Sb ug/g). While in the study by Watt an ATO exposure of 4.2 $mg/m^3$ induced a tumor incidence 61.7 % in female rats (only sex studied) and 0% in swine (located in the same chamber). The fact that tumors were observed at such disparate incidence rates compared to the exposure concentrations and in only one gender is peculiar. However, it is strongly believed that the 4.2 $mg/m^3$ exposure reported by Watt was an error and that the animals were likely exposed to significantly more test material. In addition, the fact that the third study by Newton *et al.* (1994) did not reveal the same potential indicates that ATO may not be carcinogenic or is acting by a dust overload mechanism rather than by some direct genotoxic mechanisms. Thus, the IAOIA believes that a new study conducted by the NTP following current guidelines may help elucidate the mode of action if tumors can be generated.

Furthermore, such a study should assess chronic, 2-year inhalation exposures in rats, with three exposure concentrations, the highest exposure being at the MTD (defined as ~doubling particle retention half time), and the lowest showing a minimal or no response. The full design in terms of endpoints should be very carefully planned such that inflammatory, cell-proliferative, and genotoxic endpoints are included, together with detailed evaluation of pulmonary retention kinetics and particle size characteristics. A negative ($TiO_2$) and positive (crystalline $SiO_2$) control particle (one concentration only) should also be included. This would provide a robust assessment, which would further help resolve the question of "mode of action".

While industrial exposures to ATO are primarily by inhalation, we understand the NTP is also considering conducting a study utilizing an oral route of exposure. This route is important in industrial settings following inhalation of non-respirable dust as it is transported to the GI tract, and is pertinent to the general public from consumption of antimony that may be present in food and drinking water.

The IAOIA can confirm that nanoscale materials are not used in flame retardant applications. The particle size range of all formulations of ATO has been determined by the manufacturers and is based on eight different commercial grades of ATO produced in median physical particle size ranges of 0.84 – 5.96 µm as demonstrated upon experimental determination using state-of-the-art techniques. Furthermore, for the prediction of deposition behaviour in the respiratory tract, corresponding mass median aerodynamic diameters were obtained for the same products, ranging from 4.1 – 37 µm (EBRC, 2005). Therefore, based on the dusting characteristics of ATO, the relevant particle size range for workplace exposure considerations is 4.1 – 37 µm.

Finally, in response to the request for toxicological data and other supporting background information on the nominated substances, the IAOIA would like to submit the following studies:

Whitwell, 2005. Rat micronucleus and chromosomal aberration study of ATO in bone marrow of rat. (to be provided once finalized)
de Bie et al., 2005. Biodistribution study of ATO in the rat.
Newton et al., 2004 Developmental Inhalation toxicity study of ATO in the rat
EBRC. Final Report, Dustiness and particle size testing, Diantimony trioxide. EBRC Consulting GmbH, Hannover (D), 01 November 2005

If you have any questions or other concerns please do not hesitate to phone me at 510-748-8999 or email tserex@bbl-inc.com.

Sincerely yours,

Tessa L. Serex

Tessa L. Serex, Ph.D., D.A.B.T.
Toxicologist
and Science Advisor to the IAOIA

Cc: Dieter Drohmann
Karine Van de Velde
James Deyo
John Biesemeier

MPI RESEARCH

# AN INHALATION DEVELOPMENTAL TOXICITY STUDY IN RATS WITH ANTIMONY TRIOXIDE

| | |
|---|---|
| TEST ARTICLE: | Antimony trioxide |
| TESTING FACILITY: | MPI Research, Inc.<br>54943 North Main Street<br>Mattawan, Michigan 49071-9399 |
| STUDY NUMBER: | 952-002 |
| STUDY DIRECTOR: | Raymond E. Schroeder, M.S., D.A.B.T. |
| SPONSOR ADDRESS: | International Antimony Oxide Association<br>c/o Latham & Watkins<br>Suite 1300<br>1001 Pennsylvania Ave, N.W.<br>Washington, D.C. 20004-2505 |
| SPONSOR REPRESENTATIVE: | Tessa L. Serex, Ph.D. |
| DATE OF STUDY COMPLETION: | |

## STATEMENT OF COMPLIANCE

This nonclinical laboratory study was conducted in accordance with the United States Environmental Protection Agency (EPA) Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Good Laboratory Practice (GLP) Standards, 40 Code of Federal Regulations (CFR) Part 160, Toxic Substance Control Act (TSCA) GLP Standards, 40 CFR Part 792, and Organization for Economic Cooperation and Development (OECD) Principles of GLP (C(81)30(Final)Annex 2), except that the Sponsor has not provided documentation on the purity, stability, and other pertinent information on the batch of test article. The diet and water analyses performed by Chemical Solutions, Mechanicsburg, Pennsylvania, were conducted in accordance with Good Manufacturing Practices (GMP) Standards, 21 CFR Parts 210 and 211. Deviations from the protocol are presented in Appendix P. This report accurately reflects the raw data obtained during the performance of the study.

_____ _____

Raymond E. Schroeder, M.S., D.A.B.T. Date
Senior Study Director

## SIGNATURE

This report is being submitted by the following personnel.

Raymond E. Schroeder, M.S., D.A.B.T.
Senior Study Director

Date

## MPI RESEARCH KEY PERSONNEL

| | |
|---|---|
| **Chairman, CEO** | William U. Parfet, M.B.A. |
| **President, Chief Operating Officer** | William M. Harrison, B.S. |
| **Executive Vice President, Director of Research** | James Laveglia, Ph.D. |
| **Study Director** | Raymond E. Schroeder, M.S., D.A.B.T.<br>Senior Study Director |
| **Alternate Contact** | Paul E. Newton, Ph.D., D.A.B.T.<br>Director, Inhalation Toxicology and DART |
| **Laboratory Operations** | Benjie A. Culp, A.L.A.T.<br>Associate Director, Toxicology Services |
| | Andrew J. Terpstra<br>Project Leader, Toxicology Services |
| **Test Material Control** | Mary C. Whiting<br>Manager, Test Material Control |
| **Clinical Laboratory Medicine** | Allan G. Manus, D.V.M., M.S., D.A.C.L.A.M.<br>Director, Clinical Laboratory Medicine |
| **Pathology Division** | Theodore W. Slone, Jr., D.V.M., D.A.C.V.P.<br>Director, Pathology |
| | Catherine L. Scott, B.A., H.T. (A.S.C.P.), A.L.A.T.<br>Director, Pathology Services |
| **Report Services** | Mary Ann Scott, B.S.<br>Director, Report Services |
| | Meleia M. Evans, A.A.<br>Study Coordinator, Report Services |
| **Biostatistics and Information Science** | Helen M. Chmiel, M.S.<br>Senior Information/Biostatistical Scientist |
| **Quality Assurance** | Matthew A. Foster, B.S., RQAP-GLP<br>Manager, Quality Assurance |
| | Geoffrey E. Groff, B.S., RQAP-GLP<br>Auditor, Quality Assurance |

## TABLE OF CONTENTS

## TABLE OF CONTENTS

## 1. QUALITY ASSURANCE STATEMENT

Below are the inspections conducted by the Quality Assurance Department and the dates the inspections were reported to the Study Director and Management.

| Date(s) of Inspection | Study Phase Inspected | Date(s) Reported to Study Director/Management |
|---|---|---|
| 1/21/03, 2/18/03 | Protocol | 2/19/03, 5/13/03 |
| 2/25/03 | Test Material Administration | 2/25/03, 3/5/03 |
| 3/19/03 | Uterine Examinations | 4/3/03 |
| 3/19/03 | Protocol Amendment 1 | 4/3/03 |
| 5/2/03 to 5/13/03 | Data Review | 5/13/03 |
| 5/2/03 to 5/13/03 | Data Review | 5/13/03 |
| 5/2/03 to 5/13/03 | Report Review | 5/13/03 |
| 7/22/03 | Protocol Amendment 2 | 9/2/03 |
| 8/31/03, 9/2/03 | Report Review | 9/2/03 |
| 8/12/03 to 8/18/03 | Data Review | 9/2/03 |

Geoffrey E. Groff, B.S., RQAP-GLP
Auditor, Quality Assurance

Date

## 2. SUMMARY

This inhalation developmental toxicity study was conducted for the International Antimony Oxide Association to determine the developmental toxicity, including the teratogenic potential, of the test article, antimony trixoide, in rats. This study consisted of three treatment groups and one control (clean air) group, each containing 26 Sprague-Dawley [Crl: CD® (SD) IGS BR] female rats. The females were mated in-house to untreated male rats of the same strain. The day on which evidence of mating (vaginal plug and/or sperm) was observed was considered Day 0 of gestation. The mated female rats in each treatment group received the test article, antimony trioxide, by nose-only inhalation exposure for six hours per day from Days 0 through 19 of gestation. Targeted concentration levels were 1.5, 3.0, and 6.0 mg/$M^3$ and mean analytical exposure levels delivered were 2.6, 4.4, and 6.3 mg/$M^3$, respectively. The mated control females received clean air by the same procedure and dosing regimen as the treated females.

Observations of the dams included clinical signs conducted daily following exposures, gestation body weights, and gestation food consumption. Litters were delivered by cesarean section on Day 20 of gestation and gravid uterine weights were recorded. The total number of corpora lutea on each ovary and the number of implantations, resorptions, and fetuses on each uterine horn were recorded. Dams were necropsied and the lungs, nasopharyngeal tissue, and gross lesions preserved in 10% neutral buffered formalin. The lungs and brain were weighed and the lungs then infused via the trachea with formalin. Fetuses were weighed individually, sexed externally, and measured for crown-rump distance. All fetuses were given a gross external examination. Approximately one-half of the fetuses in each litter were placed in Bouin's solution for visceral examination and the remaining fetuses were fixed in alcohol and processed for skeletal examination. Fetal external, visceral, and skeletal findings were classified as malformations or developmental variations. Subsequently, based on organ weight changes, the lungs of 10 females/group randomly selected were processed for histopathological examination.

Particle size represented by the mass median aerodynamic diameters and geometric standard deviations ranged from 1.59 to 1.82 μM and 1.713 to 1.744, respectively.

The only maternal toxicity seen was an increase in lung weights, absolute and relative to brain weights. These effects were seen at all exposure levels evaluated (2.6, 4.4, and 6.3 mg/$M^3$). Absolute lung weights were 24.2%, 31.1%, and 38.6% heavier than control in the 2.6, 4.4, and 6.3 mg/$M^3$ groups, respectively, and lung weights relative to brain weights were 20.2, 26.3%, and 34.8% heavier, respectively. The responses were dose-related and differences from controls for each group were statistically significant.

Test article-related microscopic findings were observed in the lungs of all animals at all exposure levels. The primary test article-related microscopic change was a diffuse accumulation of pigmented alveolar macrophages which likely reflected phagocytosis and accumulation of the test article particulate matter. Accumulations of pigmented macrophages and associated inflammation were likely the cause of the increased lung weights of treated animals compared to controls.

No animals died during the study and no effect of treatment was evident from maternal clinical examinations, gestation body weight, or food consumption. Likewise, no effect of treatment was evident from maternal macroscopic findings, Day 20 gestation uterine implantation data, fetal sex ratios, fetal body weights, fetal crown rump-distance data or fetal examinations (external, visceral, or skeletal).

In this rat inhalation developmental toxicity study with antimony trioxide the Lowest Observable Adverse Effect Level (LOAEL) for maternal toxicity was 2.6 $mg/M^3$. This LOAEL was based on an increase in lung weights both absolute and relative to brain weights at all exposure levels evaluated (2.6, 4.4, and 6.3 $mg/M^3$). The changes were dose responsive and differed statistically from controls. The No-Observed-Effect Level (NOEL) for developmental toxicity was 6.3 $mg/M^3$, the highest exposure level evaluated.

## 3. INTRODUCTION

The study described in this report was conducted in accordance with Standard Operating Procedures (SOP) and the protocol as approved by the Sponsor. This study was based on the draft guideline published in the US EPA Health Effects Test Guidelines, Inhalation Developmental Toxicity Study, Office of Prevention, Pesticide, and Toxic Substances (OPPTS) 870.3600, issued June 1996 and the OECD Guideline Number 414, Prenatal Developmental Toxicity Study (dated January 22, 2001). Procedures pertinent to this study are described in this report. The protocol and amendment are presented in Appendix O.

### 3.1. Objective

The objective of this study was to determine the developmental toxicity, including the teratogenic potential, of the test article, antimony trioxide, in rats.

### 3.2. Species Selection

The current state of scientific knowledge does not provide any acceptable alternatives, *in vitro* or otherwise, to the use of live animals to accomplish the purpose of this study. The rat is a universally used model for evaluating developmental toxicity of various classes of chemicals and for which there is a large historical database. Historical control data are presented in Appendix N.

### 3.3. Justification for Number on Study

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards, and in consideration of applicable regulatory requirements.

### 3.4. Study Schedule

| | |
|---|---|
| Protocol Approved by the Sponsor: | December 20, 2002 |
| Study Initiation Date (protocol signed by Study Director): | December 20, 2002 |
| Experimental Start Date: | February 25, 2003 |
| Experimental Termination Date: | March 30, 2003 |
| Draft Report: | July 15, 2003 |

# 4. MATERIALS AND METHODS

## 4.1. Test Article Information

### 4.1.1. Test Article Receipt

Pertinent test article information and the Certificate of Analysis for the test article are presented in Appendix A.

### 4.1.2. Test Article Preparation

The test article was used as received from the Sponsor and no adjustment was made for purity. The test article was administered neat (undiluted).

### 4.1.3. Reserve Sample and Test Article Disposition

A reserve sample from the lot of test article used in this study was taken and archived. Any remaining antimony trioxide may be used for additional testing and then returned to the Sponsor.

## 4.2. Experimental Design

### 4.2.1. Animal Acquisition and Acclimation

On February 17, 2003, a total of 50 male and 140 female Sprague-Dawley [Crl: CD® (SD)IGS BR] rats were received from Charles River Laboratories, Portage, Michigan. All rats were approximately nine weeks old at arrival. The male rats were utilized for mating purposes only and body weights were not recorded. Only females with positive evidence of mating were selected for study and were weighed on Day 0 of gestation prior to test article exposure. Day 0 of gestation was defined as the day on which evidence of copulation (vaginal plug and/or sperm) was observed. The females were approximately 10 weeks old and weighed between 193 to 270 grams on Day 0 of gestation. During the one-week acclimation period prior to mating, all rats were observed daily for any clinical signs of disease.

### 4.2.2. Randomization, Assignment to Study, and Maintenance

Mated female rats were given a clinical examination on Day 0 of gestation and only females considered suitable, based on the results of these examinations, were included in the selection process. Animals were generally sorted into treatment groups using a simple randomization procedure. Extra rats obtained but not used on study, were euthanized via carbon dioxide inhalation and discarded. One hundred and four mated female rats were assigned to the treated or control groups as described in the table on the following page.

| Group Assignment | | | |
|---|---|---|---|
| Group Number | Target Exposure Level ($mg/M^3$) | Actual Analytical[a,b] Exposure Level ($mg/M^3$) | Number of Mated Female Rats |
| 1 | 0 | 0 | 26 |
| 2 | 1.5 | 2.6 | 26 |
| 3 | 3.0 | 4.4 | 26 |
| 4 | 6.0 | 6.3 | 26 |

[a]Represents mean of mean daily analytical exposure levels over the entire study.
[b]The mean analytical exposure levels are used in the presentation of all summary tables and appended individual data within the report.

Each female rat was assigned an animal number and implanted with a microchip bearing a unique identification number. Each cage was identified by the study number, animal number, group number, and sex. The individual animal number plus the study number comprised a unique identification for each rat. Animal identification was verified during the conduct of the study.

Throughout the study, all rats were kept in an environmentally controlled room. Temperature and relative humidity in the animal room were monitored and recorded daily and maintained between 65 to 70°F and 31 to 70%, respectively. Fluorescent lighting was provided for approximately 12 hours per day. From acclimation until euthanasia, the rats were individually housed in suspended, stainless steel, wire-mesh type cages, except during mating when the females were housed in similar cages with males (1:1).

Diet (meal Lab Diet®Certified Rodent Diet® #5002, PMI Nutrition International, Inc., St. Louis, Missouri) and tap water were available *ad libitum* during non-exposure periods. Water was supplied using an automatic watering system. Documentation of lot numbers of the basal diet used during the study is retained in the study file. Analytical certifications of each diet lot were performed by the manufacturer and are maintained in the Archives. The water supply is monitored for specified contaminants at periodic intervals according to SOP. The Study Director is not aware of any potential contaminants likely to be present in the diet or water that would interfere with the results of this study. Additionally, a sample each of diet and water were collected and analyzed for total antimony. These analyses were performed by Chemical Solutions, Mechanicsburg, Pennsylvania according to Good Manufacturing Practices (GMP). Data from these analyses are presented in Appendix A.

### 4.2.3. Test Article and Sham Control Administration

#### 4.2.3.1. Justification for Route of Administration

Inhalation is one of the potential routes of human exposure to this test article.

#### 4.2.3.2. Justification of Exposure Levels and Duration of Treatment

The exposure levels were selected in consultation with the Sponsor on the basis of available data from previous studies. Animals were treated from fertilization (Day 0 of gestation) to Day 19, one day prior to scheduled euthanasia and laparohysterectomy. This dosing regimen was proposed to identify possible effects on preimplantation loss of the fertilized ova as well as effects on the developing fetus *in utero*.

#### 4.2.3.3. Animal Exposure

Inhalation exposure data are presented in Appendix B.

For the exposure, each animal was removed from the home cage and placed in a nose-only restraint tube. The nose of each animal protruded from a small opening in the conical end of the tube. The conical end of the tube was inserted into the chamber prior to generation of test atmosphere. Food and water was not available to the animals during the exposure period. Following the required exposure duration, the animals were returned to the appropriate individual home cages where food and water were available.

The exposures were conducted in a 63 L stainless steel and acrylic nose-only exposure chamber with a stainless steel baffle (see Figure 1). A chamber airflow of at least 0.6 L per minute per animal supplied by the generation system resulted in at least 10 chamber air changes per hour and an oxygen level at or above 19%. The chamber was maintained to the maximum extent possible at a mean temperature between 18 to 24°C and a mean relative humidity between 3 to 7%. Chamber temperature, percent relative humidity, and airflow rate were monitored continuously and recorded at 30 minute intervals during the exposure period. The treated animals were exposed to the test article approximately six hours per day, from Day 0 to 19 of gestation at concentrations of 2.6, 4.4, and 6.3 $mg/M^{-3}$.

Test article exposure began on Day 0 of gestation and continued through Day 19 of gestation. The test article was generated into the breathing air of the treated animals. Dust aerosol atmospheres of the test article were generated using a Wright Dust feeder (WDF) as the primary device in the generation system. Prior to any generation, the test article was packed into a cylindrical holder (cup) with high pressure to provide a compact uniform test article surface. A scraping blade in the WDF rotated over the test article surface in the cup, removing small amounts of test article. The test article that was dislodged by the scraping blade was entrained in the air stream, passed through the WDF, and transported out of the WDF into the elutriation chamber prior to entering the exposure chamber. Dilution air was introduced into the chamber as necessary to increase the chamber airflow and achieve correct chamber concentration (see Figure 2). The test exposure atmosphere generation system employed was determined during pre-study trials to determine the optimal equipment and operating conditions to generate accurate and precise exposure levels.

The control animals were exposed to clean air by the same exposure regimen as the treated groups except that the test article was not introduced into the chamber and a WDF was not used; compressed air was introduced into the chamber from the opening in the top.

### 4.2.4. Chamber Monitoring

#### 4.2.4.1. Nominal Concentration

The amount of test article delivered by the generation system during the exposure was divided by the total volume of air passing through the chamber to give the nominal concentration.

#### 4.2.4.2. Analytical Concentration

Chamber atmosphere samples for determination of the test article exposure level were collected (one sample/exposure in the air control group and four samples/exposure in the test article exposure groups). The samples were withdrawn from the exposure chamber through metricel membrane filters mounted on an open-faced filter holder (see Figure 3). The gravimetric concentrations were calculated with the use of atomic absorption spectroscopy.

#### 4.2.4.3. Homogeneity

Prior to initiation of animal exposures, samples were taken to show that the test article was evenly distributed from port to port on the nose-only chamber.

#### 4.2.4.4. Particle Size Distribution Analyses

One particle size distribution was performed at least once during each exposure using the TSI Aerodynamic Particle Sizer (APS), to determine the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of any aerosol present (see Figure 3). The TSI APS operated by accelerating particles through a nozzle and measuring the time required for each particle to pass between two closely-spaced laser beams. Small particles accelerated rapidly, while large particles lagged behind due to increased inertia. The time-of-flight data were calibrated with unit density ($1 g/cm^3$) spherical particles so that the particles collected were sized aerodynamically equivalent to the particles regardless of their physical size, shape, or density. The instrument consisted of the APS, a diluter (model 3302), and a computer. The diluter reduced the particle concentration of high concentration aerosols. If the aerosol concentration was too high, coincidence counting would have occurred. To keep the coincidence error below 5%, the particle concentration was maintained at less than 2850 particles per cubic centimeter for 0.5 μm particles, or 1193 particles per cubic centimeter for 10 μm particles.

### 4.3. In-life Examinations

#### 4.3.1. Mortality and Cageside Observations

All rats were observed twice each day, seven days a week, for morbidity, mortality, signs of injury, and availability of food and water.

#### 4.3.2. Detailed Clinical Examinations

Daily from Days 0 through 20 of gestation, each rat was removed from the cage and given a detailed clinical examination. During the treatment period, these examinations were conducted as animals were removed from the exposure chambers. The first group of animals examined was randomized each day of the exposure period.

### 4.3.3. Body Weights and Body Weight Changes

Individual body weights were recorded on Days 0, 3, 6, 9, 12, 15, 18, and 20 of gestation. Individual body weight change was calculated for the following gestation day intervals: 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 0-20. Adjusted body weight (Day 20 gestation body weight minus the gravid uterine weight) and adjusted body weight change (Days 0-20 of gestation) were also calculated. Body weights recorded at arrival are not reported, but are maintained in the study file.

### 4.3.4. Food Consumption

Food consumption was recorded on the corresponding body weight days and calculated for the following intervals: Days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 0-20 of gestation.

### 4.3.5. Clinical Pathology

Blood samples (5 mL/sample) were collected via cardiac puncture, after carbon dioxide inhalation, from 10 randomly selected pregnant animals per group on Day 20 of gestation. The samples were collected into tubes containing EDTA anticoagulant and separated into red blood cells (RBC) and plasma components. The RBC component was refrigerated at 2-8°C and shipped for analysis of concentrations of bound antimony. The plasma samples were stored frozen (-20°C) until it was determined that these analyses were not required.

All analytical work was conducted by National Medical Services (NMS), Willow Grove, Pennsylvania, using an analytical method developed by NMS. The work performed in conjunction with this study was conducted in compliance with GLP regulations and subject to review by the Quality Assurance Unit of NMS. Method validation for antimony was conducted using rat control RBCs. A tabular presentation of RBC antimony levels and a Quality Assurance Statement will be presented in Appendix G.

## 4.4. Postmortem Study Evaluations

### 4.4.1. Ovarian and Uterine Examinations

On Day 20 of gestation, each female was euthanized by carbon dioxide inhalation and immediately subjected to a laparohysterectomy. The skin was reflected from a ventral midline incision to examine mammary tissue and locate any subcutaneous masses. The abdominal cavity was then opened and the uterus was exposed. The uterus was excised, the gravid uterine weight recorded. Beginning at the distal end of the left uterine horn, the location of viable and nonviable fetuses, early and late resorptions for each uterine horn, position of the cervix, and the total number of implantations were recorded. The number of corpora lutea on each ovary was also recorded. The fetuses were removed by making a dorsal incision longitudinally along both uterine horns. The embryonic membrane of each fetus was gently removed, and each fetus was pulled away from the placenta, fully extending the umbilical cord. The placentae were grossly examined. Before the umbilical cord was cut on each fetus, it was momentarily clamped with forceps to prevent bleeding and promote clotting. After examination, the uterus was discarded. Each implant was characterized as either a viable or nonviable fetus, or either an early or late resorption. Viable fetuses

responded to touch while nonviable fetuses did not and showed no signs of autolysis. Early resorptions were characterized as implantation sites consisting of tissues but no recognizable fetal characteristics, while late resorptions displayed recognizable fetal characteristics, but undergoing the process of autolysis.

Uteri from females that appeared nongravid were opened and placed in 10% ammonium sulfide solution for detection of implantation sites.[1] If no foci were seen, the female was considered not pregnant and all data was excluded from statistical analysis.

### 4.4.2. Macroscopic

A complete necropsy was performed on all dams under procedures approved by a veterinary pathologist. Special emphasis was placed on structural abnormalities or pathologic changes that may have influenced the pregnancy. The lungs, nasopharyngeal tissue, and gross lesions from the dams were saved in 10% neutral buffered formalin. After weighing, the lungs were infused via the trachea with formalin. The carcasses were then discarded. Collection of gross lesions and/or target organs necessitated collection of sufficient corresponding tissues from controls for comparison purposes. A glossary of macroscopic terms used in this study is included in this report.

### 4.4.3. Organ Weights

The lungs and brains were weighed. The brain weights were used to calculate lung/brain weight ratios, but the brains were not saved.

### 4.4.4. Microscopic

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections was performed on the lungs of 10 randomly selected pregnant females per group. One section/lobe/animal (5 sections/animal) were examined.

### 4.4.5. Teratologic Examinations

Fetuses were individually weighed, measured for crown-rump distance, sexed externally, tagged for identification, and examined for external malformations and variations. Approximately one-half of the fetuses in each litter were placed in Bouin's solution for subsequent soft tissue examination using the Wilson razor-blade sectioning technique.[2] The remaining fetuses were fixed in alcohol, processed for Alizarin Red S and Alcian blue staining, and cleared with glycerin for subsequent skeletal examination of bone and cartilage.[3] Fetal findings were classified as malformations or developmental variations under the supervision of a developmental toxicologist.

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[1] Kopf, R., Lorenz, D., and Salewski, E. (1964). The effects of thalidomide on the fertility of rats studied in two generations. *Naunyn Schmiedebergs Arch. Pharmacol.* **247**, 121-135.

[2] Wilson, J.G. (1965). Methods for administering agents and detecting malformations in experimental animals. J.G. Wilson and J. Warkany, eds. *Teratology-Principles and Techniques*. The University of Chicago Press, Chicago Illinois, pp. 262-277.

[3] Kimmel, C.A. and Trammell, C. (1981). A rapid procedure for routine double staining of cartilage and bone in fetal and adult animals. *Stain Technology*, **56**, 271-273.

### 4.5. Statistics

The table below defines the sets of comparisons used in the statistical analyses described in this section.

| Statistical Comparisons | |
|---|---|
| Control Group | Treatment Groups |
| 1 | 2, 3, 4 |

The endpoints that were analyzed and the methods of analysis that were employed are presented in the table on the following page.

| Statistical Analysis Methods | |
|---|---|
| **Endpoint** | **Analysis** |
| **Parental In-life Data** | |
| Gestation Body Weights | Group Pair-wise Comparisons |
| Gestation Body Weight Changes | Group Pair-wise Comparisons |
| Gestation Food Consumption | Group Pair-wise Comparisons |
| Adjusted Body Weights | Group Pair-wise Comparisons |
| Adjusted Body Weight Changes (Days 0-20) | Group Pair-wise Comparisons |
| RBC antimony levels | Group Pair-wise Comparisons |
| **Fertility Indices** | |
| Pregnancy Index | Fisher's Exact Test |
| **Pathology** | |
| Absolute lung and brain weights and lung weights relative to brain weights | Group Pair-wise Comparisons |
| **Uterine and Ovarian Exam** | |
| Gravid Uterine Weights | Group Pair-wise Comparisons |
| Corpora Lutea/dam | Group Pair-wise Comparisons |
| Total Implantations/dam | Group Pair-wise Comparisons |
| Fetal Sex Ratio (% males/litter) | Arcsin-Square-Root Transformation |
| Litter Size/dam | Group Pair-wise Comparisons |
| Viable Fetuses/dam | Group Pair-wise Comparisons |
| Nonviable Fetuses/dam | Descriptive Statistics |
| Total Number Resorptions/dam | Group Pair-wise Comparisons |
| Number Early Resorptions/dam | Group Pair-wise Comparisons |
| Number Late Resorptions/dam | Group Pair-wise Comparisons |
| % Preimplantation Loss | Arcsin-Square-Root Transformation |
| % Postimplantation Loss | Arcsin-Square-Root Transformation |
| Mean Fetal Body Weights | Covariate Analysis |
| Mean Crown-rump Distance | Group Pair-wise Comparisons |
| Individual Malformations by finding and exam type (external, visceral, and skeletal) – litter incidence[a] | Fisher's Exact Test |
| Individual Variations by finding and exam type (external, visceral, and skeletal) – litter incidence[a] | Fisher's Exact Test |
| Total Malformations (external, visceral, and skeletal combined) – litter incidence[a] | Fisher's Exact Test |

[a]Fetal and litter incidences were reported, but only the litter incidences were statistically analyzed.

### 4.5.1. Group Pair-wise Comparisons

For each specified endpoint and for all collection intervals, Levene's test[4] was used to assess homogeneity of group variances. If Levene's test was not significant ($p \geq 0.01$), Dunnett's test[5] was used to compare each treatment group with the control group. If Levene's test was significant ($p < 0.01$), comparisons with the control group were made using Welch's t-test[6] with a Bonferroni correction. Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests unless indicated otherwise.

### 4.5.2. Arcsin-Square-Root Transformation

Data comprised of percent values were transformed using the arcsin of the square root.[7] The analysis described in Section 4.5.1. Group Pair-wise Comparisons was then used to analyze the transformed percentage values.

### 4.5.3. Fisher's Exact Test

Each treatment group was compared to the control group using a Fisher's exact test with a Bonferroni correction. Results were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests unless indicated otherwise.

### 4.5.4. Covariate Analysis

For the mean of fetal body weights, a test of assumptions[8] for Analysis of Covariance was performed to determine whether litter size would be included as a covariate in the model. If the assumptions on the Analysis of Covariance were met, the model with the covariate was used to test for a difference from control using the Dunnett's test.[5] If the assumptions for the Analysis of Covariance were not met, the endpoint was analyzed in the manner described in Section 4.5.1. Group Pair-wise Comparisons. Each treatment group was compared with the control group and results were reported at the 0.05 and 0.01 significance levels. Endpoints were analyzed using two-tailed tests.

Whether the covariate was included or not, the LSMEANS, which are the adjusted means, were displayed on the summary table. If the covariate was used in the analysis, the adjusted means can be used in the interpretation of the analysis. If the covariate was not used in the analysis, the LSMEANS were equivalent to the means.

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[4] Milliken, G.A. and Johnson, D.E. (1992). *Analysis of Messy Data.* Chapman and Hall, London.
[5] Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association* **56**, 52-64.
[6] Welch, B.L. (1937). The significance of difference between two means when the population variances are unequal. *Biometrika* **29**, 350-362.
[7] Steel, R.G.D. and Torrie, J.H. (1980). *Principles and Procedures of Statistics. A Biometrical Approach.* McGraw-Hill, New York.
[8] Littell, R.C., Milliken, G.A., Stroup, W.W., and Wolfinger, R.D. (1996), *SAS System for Mixed Models.* SAS Institute Inc., Cary, North Carolina.

### 4.5.5. Descriptive Statistics

Descriptive statistics consisted of means, standard deviations, and number of animals for each group and time period.

## 4.6. Computer Systems

The following computer systems were used during the conduct of this study.

| Computer Systems | |
|---|---|
| In-life Systems: | Provantis™ |
| Randomization: | Provantis™ |
| Developmental and Reproduction System: | Provantis™ |
| Pathology: | Provantis™ |
| Statistical Analysis: | SAS |
| Reporting: | SAS and Microsoft Office Professional |

## 4.7. Data and Specimen Retention

All raw data, documentation, records, protocol, reserve samples, specimens, wet tissues, and the final report generated as a result of this study will be retained at MPI Research, Inc., or an approved archive facility contracted by MPI Research, Inc., for a period of one year following completion of the study (final report issue date). Retention of materials after the time stated above will be subject to future contractual agreements with the Sponsor.

# 5. RESULTS AND DISCUSSION

## 5.1. Chamber Monitoring

### 5.1.1. Concentration Analysis

The gravimetric chamber concentrations are summarized in Appendix B and the mean exposure levels are summarized below.

| Chamber Atmosphere Monitoring | | | |
|---|---|---|---|
| Group | Target Concentration ($mg/M^3$) | Mean Chamber Concentration ($mg/M^3$) ± SD | Mean Nominal Concentration ($mg/M^3$) ± SD |
| 1 | 0 | 0 ± NA | NA |
| 2 | 1.5 | 2.6 ± 2.43 | 54.3 ± 40.08 |
| 3 | 3.0 | 4.4 ± 3.88 | 40.1 ± 25.15 |
| 4 | 6.0 | 6.3 ± 4.18 | 48.2 ± 21.85 |
| SD – Standard Deviation<br>NA – Not Applicable | | | |

In an attempt to control the exposures at these very low levels, the test article was generated at a higher more stable level and then diluted down to achieve the targeted exposure level. As a result the nominal exposure levels were higher than the actual measured levels. In addition, this difference also represents the normal losses seen with deposition of the test article on the walls within the chamber and generation system.

### 5.1.2. Chamber Environment

Temperature, relative humidity, and chamber airflow were monitored continuously and recorded approximately every 30 minutes during the exposure. Temperature and relative humidity measurements are summarized below and also presented in Appendix B. Chamber airflow data were recorded in the study data (individual data not presented) and summarized below.

| Chamber Environment Conditions | | | | | | |
|---|---|---|---|---|---|---|
| Group | Temperature (°C) | | Relative Humidity (%) | | Chamber Airflow (L/min) | |
| | Mean | SD | Mean | SD | Mean | SD |
| 1 | 21 | 1.3 | 7 | 2.1 | 34.0 | 0.00 |
| 2 | 22 | 1.3 | 3 | 0.5 | 25.1 | 2.78 |
| 3 | 22 | 1.5 | 5 | 1.4 | 39.4 | 2.71 |
| 4 | 22 | 1.6 | 4 | 1.5 | 45.5 | 3.89 |
| SD - Standard Deviation | | | | | | |

### 5.1.3. Particle Size Distribution Measurement

The mass median aerodynamic diameters (MMAD) and geometric standard deviations (GSD) ranged from 1.59 to 1.82 μM and 1.713 to 1.744, respectively. The particle size distribution data are summarized below and in Appendix B.

| Particle Size Distribution Data | | |
|---|---|---|
| Group | Mean MMAD (μM) ± SD | Mean GSD ± SD |
| | | |
| 1 | NA | NA |
| 2 | 1.74 ± 0.405 | 1.744 ± 0.3189 |
| 3 | 1.82 ± 0.582 | 1.713 ± 0.3780 |
| 4 | 1.59 ± 0.151 | 1.714 ± 0.2363 |
| MMAD – Mass Median Aerodynamic Diameters<br>GSD – Geometric Standard Deviations<br>SD – Standard Deviation<br>NA – Not Applicable | | |

## 5.2. In-life Examinations

### 5.2.1. Mortality

The record of animal fate and disposition is located in Appendix C.

All animals in the control and treated groups survived to scheduled euthanasia on Day 20 of gestation.

### 5.2.2. Detailed Clinical Observations

Gestation clinical findings are summarized in Table 1 and presented individually in Appendix D.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 $mg/M^3$ was evident from the detailed clinical examinations. Findings seen in the treated groups were similar to those seen in the controls and occurred with similar frequency. Red, brown, and/or black material around the eyes, mouth, and/or nose was seen in many animals from the control and treated groups. This was attributed to restraint during exposures and the inability of animals to groom during this period.

### 5.2.3. Body Weights and Body Weight Changes

Maternal body weight and body weight change data during gestation are summarized in Tables 2 and 3, respectively, and presented individually in Appendix E.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 mg/M$^3$ was evident from gestation body weights or body weight gains. Mean body weights for the treated groups throughout gestation and mean body weight gain between each weighing interval and over the entire Gestation Day (GD) 0-20 period were comparable to controls.

### 5.2.4. Food Consumption

Maternal food consumption data during gestation are summarized in Table 4 and presented individually in Appendix F.

No adverse effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 mg/M$^3$ was evident from gestation food consumption data. In the 2.6 mg/M$^3$ group, food consumption throughout gestation and over the GD 0-20 period was comparable to controls. In the 4.4 and 6.3 mg/M$^3$ groups, food consumption was statistically higher than controls over GD 15-18, 18-20, and 0-20. These increases in food consumption corresponded with slight increases in body weight gains over these same intervals, but the differences in weight gain from controls were not statistically significant and not considered toxicologically meaningful. For all other intervals during gestation, food consumption in these groups was comparable to controls.

### 5.2.5. RBC Analytical Results

The results of the RBC analysis, performed by National Medical Services, will be presented in Appendix G.

## 5.3. Postmortem Study Evaluations

### 5.3.1. Macroscopic Observations

Maternal macroscopic observations are summarized in Table 5 and presented individually in Appendix H.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 mg/M$^3$ was evident from maternal macroscopic findings. The only finding seen at macroscopic examination of the treated females was a mass in a single female in the 4.4 mg/M$^3$ exposure group. In the absence of similar findings at the high-exposure level, this was considered spontaneous in origin and unrelated to treatment. No macroscopic findings were seen in control animals.

### 5.3.2. Organ Weight Values

Maternal organ weight values are summarized in Table 6 and presented individually in Appendix I.

A dose-related increase in lung weights, absolute and relative to brain weights, was seen in the antimony trioxide-treated groups. These differences in lung weights from controls were statistically significant and considered indicative of a treatment-related response. Absolute lung weights were 24.2%, 31.1%, and 38.6% heavier than control in the 2.6, 4.4, and 6.3

mg/$M^3$ groups, respectively, and lung weights relative to brain weights were 20.2, 26.3%, and 34.8% heavier, respectively.

### 5.3.3. Microscopic Observations

Maternal Microscopic Observations are summarized in Table 7 and presented individually in Appendix H.

Test article-related microscopic findings were observed in the lungs of all animals evaluated at all exposure levels. The primary test article-related microscopic change was a diffuse accumulation of pigmented alveolar macrophages which likely reflected phagocytosis and accumulation of the test article particulate matter. Pulmonary alveoli contained variable numbers of macrophages with abundant eosinophilic cytoplasm with minimal to moderate quantities of brown granular pigment, as well as small to moderate quantities of extracellular eosinophilic proteinaceous material containing similar pigment. Throughout the lungs, scattered foci of acute inflammation and type II cell hyperplasia were often observed. Accumulations of pigmented macrophages and associated inflammation were likely the cause of the increased lung weights of treated animals compared to controls.

The microscopic finding of increased numbers of alveolar macrophages containing foreign material noted in the current study is similar to findings observed in previous subacute and chronic inhalation studies of antimony trioxide in Fischer rats[9]. However, as would be expected, the inflammation and type II cell hyperplasia noted in the current study was generally of acute to subacute duration as opposed to the granulomatous inflammation and interstitial fibrosis observed in the previous studies.

Test article-related microscopic findings are summarized in the table on the following page.

[9] Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, and Rubin LF. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol 1994; 22: 561-6.

| Test Article-Related Microscopic Findings<br>Terminal<br>Females | | | | | |
|---|---|---|---|---|---|
| Exposure Level: mg/M$^3$ | | 0 | 2.6 | 4.4 | 6.3 |
| Number Examined | | 10 | 10 | 10 | 10 |
| **Lung** | | (10) | (10) | (10) | (10) |
| Hyperplasia, type II cell, | | 0 | 5 | 4 | 5 |
| | -minimal | 0 | 2 | 4 | 3 |
| | -mild | 0 | 2 | 0 | 2 |
| | -moderate | 0 | 1 | 0 | 0 |
| Inflammation, acute, | | 0 | 7 | 4 | 6 |
| | -minimal | 0 | 4 | 4 | 4 |
| | -mild | 0 | 3 | 0 | 2 |
| Macrophages, pigmented alveolar, | | 0 | 10 | 10 | 10 |
| | -minimal | 0 | 2 | 1 | 0 |
| | -mild | 0 | 5 | 9 | 3 |
| | -moderate | 0 | 3 | 0 | 7 |

### 5.3.4. Uterine and Ovarian Examinations

Corpora lutea and uterine examination data are summarized in Table 8 and presented individually in Appendices J and K. Gravid uterine weights, adjusted Day 20 gestation body weights, and body weight changes over Days 0-20 of gestation using the adjusted body weights are summarized in Table 9, and presented individually in Appendix L.

Pregnancy rates were comparable between the control and antimony trioxide-treated groups. These rates ranged from 96.2 to 100%, and provided 25, 25, 26, and 25 GD 20 litters for evaluation in the control, 2.6, 4.4, and 6.3 mg/M$^3$ groups, respectively.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 mg/M$^3$ was evident from uterine implantation data. The mean number of corpora lutea, implantations, viable fetuses, and resorptions sites and mean pre- and postimplantation loss indices for the treated groups did not differ statistically from controls and were considered comparable between the groups. What appeared to be a slight increase in mean number of resorptions and postimplantation loss in the 6.3 mg/M$^3$ group was not considered toxicologically meaningful. These parameters did not differ statistically from controls and were within the range of recent historical control data for the laboratory (see Appendix N). Control values for postimplantation loss were outside the low range of these historical data.

Gravid uterine weights, adjusted GD 20 body weights, and adjusted body weight change GD 0-20 for the treated groups were comparable to controls. No effect of treatment was evident from these data.

### 5.3.5. Fetal Data

#### 5.3.5.1. Body Weights

Fetal body weights are summarized in Table 10 and presented individually in Appendix K.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 $mg/M^3$ was evident from fetal body weights. Mean fetal body weights distinguished by sex and for both sexes combined in the treated groups were comparable to controls. Slightly lower fetal body weights seen in a pilot study conducted at this laboratory (MPI Research Study Number 952-001) at an exposure level of 6.07 $mg/M^3$ was not seen in this study.

#### 5.3.5.2. Sex Ratio

Fetal sex ratios are summarized in Table 8. The distribution of fetuses by sex within individual litters is presented in Appendix J and the sex of individual fetuses is identified in Appendix K.

Mean fetal sex ratios (% male fetuses per litter) in the treated groups ranged from 48.0 to 49.8 and were comparable to controls (48.9).

#### 5.3.5.3. Crown-Rump Distance

Fetal crown-rump distance measurements are summarized in Table 11 and presented individually in Appendix K.

No effect of treatment with antimony trioxide at an exposure level up to and inclusive of 6.3 $mg/M^3$ was evident from fetal crown-rump distance. Fetal crown-rump distance distinguished by sex and for both sexes combined in the treated groups was comparable to controls. Slightly shorter crown rump distance measurements seen in a pilot study conducted at this laboratory (MPI Research Study Number 952-001) at an exposure level of 6.07 $mg/M^3$ was not seen in this study.

#### 5.3.5.4. External Examination

The overall incidence of fetal external malformations and variations is summarized in Table 14. Individual fetal external observations are presented in Appendix M.

No malformations or developmental variations were seen in control or treated fetuses during the external examinations.

#### 5.3.5.5. Visceral Examination

Individual fetal visceral observations are summarized in Table 12 and the overall incidence of fetal visceral malformations and variations is summarized in Table 15. Individual fetal visceral observations are presented in Appendix M.

Anophthalmia (absence of the eye) was seen in a single fetus in the 6.3 $mg/M^3$ group (litter incidence 4.0%). While this malformation has not been seen in recent historical control data for this laboratory (Appendix N), its low incidence in occurrence in this study was

considered spontaneous and unrelated to treatment. No other visceral malformations or developmental variations were seen among these fetuses. Likewise, no visceral malformations or developmental variations were seen in fetuses from the 2.6 and 4.4 mg/M$^3$ groups or in control fetuses.

### 5.3.5.6. Skeletal Examination

Individual fetal skeletal observations are summarized in Table 13 and the overall incidence of fetal skeletal malformations and variations is summarized in Table 16. Individual fetal skeletal observations are presented in Appendix M.

No skeletal malformations were seen among the control and treated fetuses. Likewise, no effect of treatment was evident from ossification variation data. There was general agreement in the types of ossification variations seen between treated and control fetuses and the litter incidences of these findings. The litter incidence for unossified metacarpals in the 4.4 mg/M$^3$ group was statistically lower than controls. However, this was not considered to represent an adverse effect of treatment or toxicologically meaningful.

### 5.3.5.7. Total Malformations

The incidence of fetuses with malformations as seen during the different evaluations (external, visceral, and skeletal) and the incidence of litters containing affected fetuses are summarized in Table 17. No malformations (external, visceral or skeletal) were seen among fetuses in the 2.6 and 4.4 mg/M$^3$ groups or control group. In the 6.3 mg/M$^3$ group, there was only one fetus with a visceral malformation (litter incidence of 4.0%) and its occurrence in this study was considered spontaneous and unrelated to treatment.

## 6. CONCLUSION

In this rat inhalation developmental toxicity study with antimony trioxide the Lowest Observable Adverse Effect level (LOAEL) for maternal toxicity was 2.6 mg/$M^3$. This LOAEL was based on an increase in lung weights both absolute and relative to brain weights at all exposure levels evaluated (2.6, 4.4, and 6.3 mg/$M^3$). The changes were dose responsive and differed statistically from controls. The No-Observed-Effect Level (NOEL) for developmental toxicity was 6.3 mg/$M^3$, the highest exposure level evaluated.

## DEVELOPMENTAL GLOSSARY

**Abnormality** - A morphologic or functional deviation from normal limits (anomaly).

**Activity** - Action or process of exerting energy.

**Cesarean Section** - Laparotomy to deliver the fetus(es) is performed on gestation day 20 (rat).

**Conception** - The onset of pregnancy; formation of a visible zygote.

**Corpora Lutea** - Ovarian follicle cells which have discharged their ova and become hypertrophied, assuming a yellow color. Regressing c. - corpora lutea in process of degeneration due to death of embryos *in utero.*

**Development** - Gradual growth or expansion, especially from a lower to a higher stage of complexity.

- Arrested Development - Cessation of the developmental process at some stage prior to its normal completion.
- Prenatal Development - That which occurs before birth.
- Postnatal Development - That which occurs after birth.

**Developmental Toxicity** - Toxicity incurred by the conceptus during development. There are four manifestations: (1) growth retardation, (2) death, (3) terata or malformation, and (4) functional deficit. The term supercedes older terms "embryotoxicity" (death, malformation) and "fetotoxicity" (death, growth retardation), thereby eliminating temporal considerations.

**Developmental Variations** - [Also formerly referred to as variations (skeletal, anatomic, homoeotic), common variants, aberrations, retardations, anomalies, deviations]. Defined recently by a regulatory agency as a "divergence beyond the usual range of structural constitution, and which may not be as severe an effect as a malformation" [EPA, *Fed. Reg.*,51 (185): 34028, 1986].

For purposes of this laboratory, variations are defined as those alterations in anatomic structure that are considered to have no significant adverse biological effect on animal health or body conformity, representing slight deviations from normal. Most examples placed in this category are minor variations in size and form of normally present ossification centers. While these are evaluated on a precise day of development, some variation is expected related to when conception and implantation actually occurred. Thus, differences in the pattern of ossification, manifested either as retardation or as acceleration of apparent osteogenesis, are common findings. Also included in this category are slight misshapening or misalignment of structures, and processes involving continued development (bilateral skeletal centers not yet fused, incomplete maturation of renal papillae, presence of vestigial structures, etc.), and development of extra ossification sites. Slight malpositioning and hypoplasia are also considered variations in development.

Developmental variations correlate in some instances with maternal and/or developmental toxicity.

**Distal** - Distant from the trunk.

**Embryo** - The early or developing stage of an organism, especially the developing product of fertilization of an egg. Its development is termed embryogenesis. The embryonic period is as follows:

| | |
|---|---|
| Rat | 9-14 days postconception |

**Fecundity Index or Pregnancy Index** -

$$\frac{\text{No. females pregnant}}{\text{No. females with evidence of mating}} \times 100$$

**Fetus** - The unborn offspring; the developing young following embryogenesis. The fetal period is as follows:

| | |
|---|---|
| Rat | 15-22 days postconception |

**Gestation** - The period of intrauterine development; conception to birth.

**Gestation Day 0** - Day in which positive evidence of mating has been ascertained.

**Gestation Duration** - The length of gestation; term of pregnancy. The duration is as follows for the common species:

| | |
|---|---|
| Rat | 21 days |

**GLPs** - Good Laboratory Practices. Legislation first enacted in June, 1979 to assure the quality and integrity of safety data filed pursuant to products regulated by the U.S. FDA. The Final Rule became effective October 5, 1987 [*Fed. Reg.*, 52 (172: 33768, 1987)]. Similar GLPs have since been adopted by the U.S. EPA (effective October 16, 1989 for pesticides, and September 18, 1989 for TSCA-regulated chemicals), Japan Koseisho (April 1, 1983) and Japan MAFF (October 1, 1984).

**Gravid** - An animal with uterine evidence of implantation which delivers a conceptus or contains developing young (pregnant).

**Implantation** - Attachment of the blastocyst to the epithelial lining of the uterus, its penetration through the epithelium, and its embedment in the compact layer of the endometrium (nidation).

It occurs after fertilization as follows:

| | |
|---|---|
| Rat | 5.5 - 6 days |

Implantation sites not discernible by placental remains may be visualized by staining of the uterus with ammonium sulfide (Kopf method, *Naunyn Schmiedebergs Arch. Pharmacol.*, 247: 121-135, 1964).

The types of implants as defined by SOP are as follows: a) viable fetus - responds to touch, b) nonviable fetus - does not respond to touch, no signs of autolysis, c) late resorption - recognizable fetal form, but undergoing autolysis, d) early resorption - implantation site, tissue has no recognizable fetal characteristics.

**Lesion** - Any pathological or traumatic discontinuity of tissue or loss of function of a part; a circumscribed area of pathologically altered tissue.

**Litter Size** - In polytocous animals, pregnancy consists of multiple offspring in the litter; this averages for the common species in our laboratory of (live + dead):

| | |
|---|---|
| Rat | 13.4 |

**Malformation** - Defective or abnormal function; anatomic or morphologic abnormality; deformity (dysmorphosis, cacomorphosis). Defined recently by a regulatory agency as "a permanent deviation which generally is incompatible with or severely detrimental to normal postnatal survival or development" [EPA, *Fed.Reg.*, 51 (185): 34028, 1986].

For practical purposes we use the following definition in this laboratory: Malformations are those structural anomalies that alter general body conformity, disrupt or interfere with body function, or are generally thought to be incompatible with life. Specific examples of processes that result in maldevelopment include marked or severe misshapening, asymmetry or irregularity of structure brought about by fusion, splitting, disarticulation, malalignment, hiatus, enlargement, lengthening, thickening, thinning, or branching. Absence (agenesia) of parts or whole structures is also considered a malformative process.

Malformations occur when normal organogenesis is interrupted.

**Mating Index –**
No. females with evidence of mating x 100
No. females paired

No. males with evidence of mating x 100
No. males paired

**Moribund** - In a state of dying.

**NOEL** - No observable effect level.

**NOAEL** - No observable adverse effect level.

**Nonviable** - A nonliving conceptus; includes early and late resorptions and dead fetuses.

**Postimplantation Loss -**
No. implantations-No. viable fetuses x 100
No. implantations

**Preimplantation Loss -**
No. corpora lutea-No. implantations x 100
No. corpora lutea

**Regressing (Corpora Lutea)** - Involution of corpora lutea in response to cessation of pregnancy maintenance.

**Reproductive Effects** - Those findings associated with reproductive parameters in generation studies. They are usually classed as primary (effects related to sex organs or reproductive capacity of adults), or secondary (changes that may be dependent upon or related to other signs of toxicity).

A tabulation of primary reproductive effects might include (Christian, *J. Am.Coll. Toxicol.,* 5: 161, 1986):

- estrous
- mating performance
- fertility
- fecundity
- duration of gestation
- delivery complications
- pathology of reproductive organs
- litter size
- litter viability at birth
- litter survival
- sex ratios of litters
- growth & functional
- development of litter, birth to weaning

**Resorption** - A conceptus which, having implanted in the uterus, subsequently died and is being, or has been, resorbed.

**SOPs** - Standard Operating Procedures.

**Spontaneous Malformations** - The normal background incidence of maldevelopment unrelated to known causes. The rate of spontaneous malformation for common species is as follows (Schardein, *Chemically Induced Birth Defects,* Dekker 1993).

Rat 0.02 - 2%

**Teratogen -** An agent or factor that causes the production of physical defects in the developing embryo. The production of defects is termed **teratogenesis**.

**Uterine Examination -** The excision of the uterus to determine pregnancy status. The location of viable and nonviable fetuses (embryos), early and late resorptions and the number of total implantations is determined through the unopened uterine wall.

**Viable -** Capable of living.

**Aerodynamic diameter** - The diameter of a unit-density sphere having the same terminal settling velocity as the particle in question. It is used to predict where in the respiratory tract such particles will deposit.

**Aerosol** - An assembly of liquid or solid particles suspended in a gaseous medium long enough to be observed and measured; generally, about 0.001-100 μm in size.

**Alveolar** - Part of the respiratory system in which gas exchange occurs; alveoli are small sacs at the end of the bronchioles.

**Breathing zone sample** - A sample taken as close as possible to the point at which the test animal inhales the exposure atmosphere.

**Cascade impactor** - A precision instrument that uses a series of impaction stages with decreasing particle cutoff size so that particles can be separated into relatively narrow intervals of aerodynamic diameter. The impactor is used for measuring the aerodynamic size distribution of an aerosol.

**Concentration** - Amount of a given test article in a given volume of air (e.g., mg/L, $mg/m^3$, or ppm.

**Cutoff particle diameter** - median diameter of a range of particle sizes which will impact on a stage of a cascade impactor; also called 50% cut point, $d_{50}$, or the effective cutoff diameter.

**Cyclone** - A device in which particles are removed by centrifugal forces in a cyclonic path.

**Desired concentration** - The target exposure level of test article (per volume unit, e.g., mg/L) selected for each exposure group.

**Dust** - Solid particles formed by erosion or other mechanical breakage of a parent material; generally consists of particles of irregular shape and larger than about 0.5 μm.

**Dust generator** - A device used to produce a dust aerosol by dispersing dry particles in the air in a controlled fashion.

**Elutriator** - A device used to separate particles by aerodynamic diameter by allowing them to settle in a moving air stream.

**Exposure day** - Defined as the day or days when an exposure was conducted for a study.

**Exposure duration** - The time interval during which the animals were exposed to the test material, e.g., 1 hour, 4 hours, etc.

**Filter** - A porous membrane or mat of fibers used to collect particles from the air.

**Fine particle** - Particles less than about 2 μm in size; term used in describing atmospheric aerosols.

**Geometric** - Refers to a size parameter on a logarithmic size scale, where a given ratio of two sizes appears as the same linear distance.

**Geometric standard deviation** - A measure of dispersion in a lognormal distribution (always ≥1).

**Inhalable** - Fraction of an aerosol that can enter the human respiratory system.

**Inhalable particles** - Those materials that are deposited anywhere in the respiratory tract.

**Lognormal size distribution** - Particle size distribution characterized by a bell-shaped or Gaussian distribution shape when plotted on a logarithmic-size scale.

**Lower respiratory tract** - Those structures of the respiratory tract below the larynx.

**Mass median aerodynamic diameter (MMAD)** - The geometric mean aerodynamic diameter. Fifty percent of the particles by weight will be smaller than the MMAD, 50% will be larger.

**Mist** - A liquid particle aerosol, typically formed by physical shearing of liquids, such as in nebulization, spraying, or bubbling.

**Monodisperse Distribution**- A distribution of particles with a single size or a small range of sizes.

**Nominal concentration** - A gross estimate of exposure concentration based upon test material usage. The total amount of test material used during a given exposure day divided by the total volume of air passed through the chamber during the exposure.

**Open-face sampler** - A filter cassette sampler with the inlet approximately the same size as the filter.

**Particle** - A small discrete object, often having a density approaching the intrinsic density of the bulk material; it may be chemically homogeneous or contain a variety of chemical species; it may consist of solid or liquid materials or both.

**Respirable fraction** - Fraction of aerosol that can reach the gas exchange region of the human respiratory system.

**Respirable particles** - Those materials that are deposited in the gas-exchange region of the lung.

**Respiratory tract** - Composed of the conducting airway including the nose, mouth, pharynx, larynx, trachea, bronchi, bronchioles and alveoli.

**$T_{99}$** - The time required for an exposure system to change from an equilibrated state to attain 99% of a new concentration level.

This time interval is referred to as "chamber equilibrium time", is usually expressed in minutes and is calculated as follows:

$$T_{99} = 4.60 \times \frac{\text{Chamber volume}}{\text{Chamber flow rate}}$$

**Upper respiratory tract** - Those structures of the respiratory tract above the larynx.

## PATHOLOGY GLOSSARY

**Hyperplasia, type II cell** – Some alveoli are lined by cuboidal type II cells.

**Inflammation, acute** - A tissue reaction characterized by a prominent accumulation of neutrophils, with or without exudate and possibly a few lymphocytes or other inflammatory cells as typically seen early in the inflammatory process. It is not pathognomonic for a specific etiology and may or may not be of toxicologic and/or pathologic significance, depending on the context in which it occurs.

**Macrophages, pigmented alveolar** - The cytoplasm of alveolar macrophages contains pigment.

**Mass** - A focal abnormal enlargement in an organ or tissue; an excessive and abnormal growth.

**Within normal limits** - Tissue considered to be normal, under the conditions of the study and considering the age, sex, and strain of the animal concerned. Alterations may be present which, under other circumstances, would be considered deviations from normal.

FIGURE 1
Chamber System

Figure 1 **CHAMBER SYSTEM**

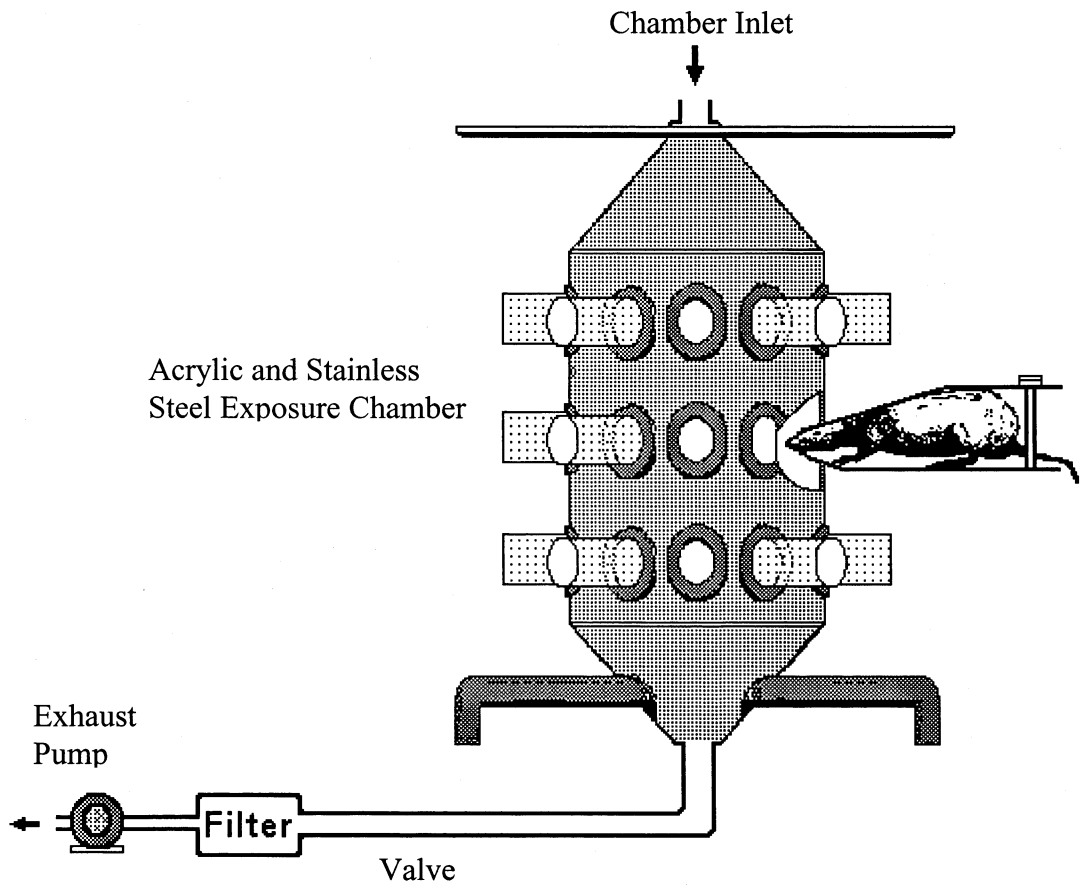


FIGURE 2
Generation System

Figure 2 **GENERATION SYSTEM**

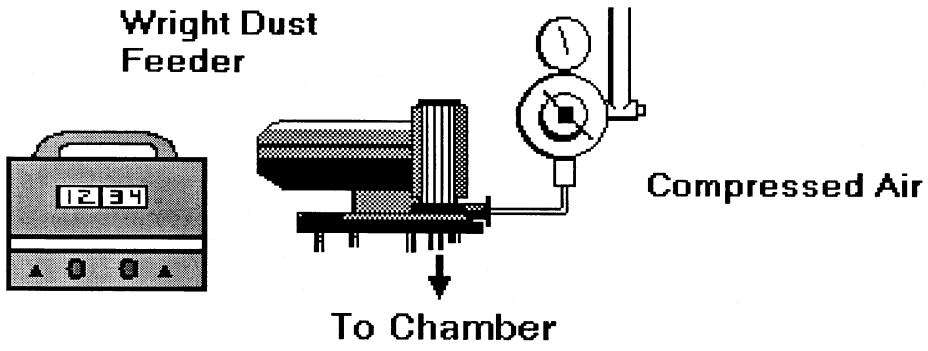


Figure 2 cont. **GENERATION SYSTEM**

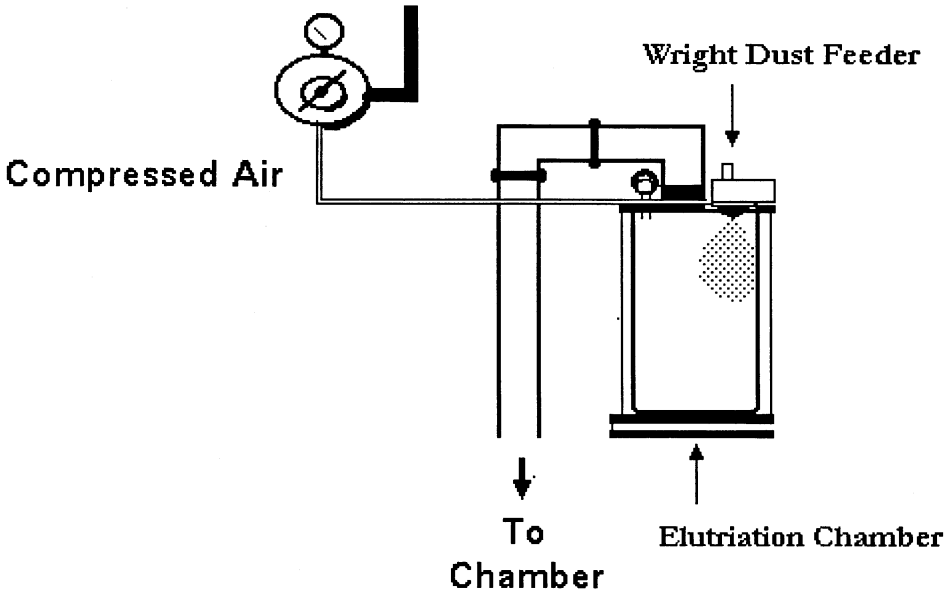
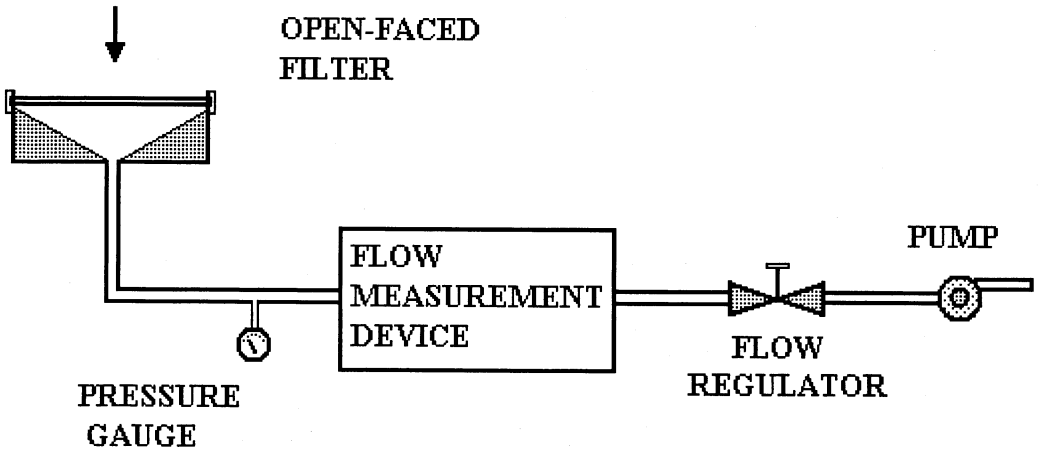


FIGURE 3
Monitoring System

Figure 3 **MONITORING SYSTEM**

**Gravimetric Concentration**




**Particle Size Distribution**

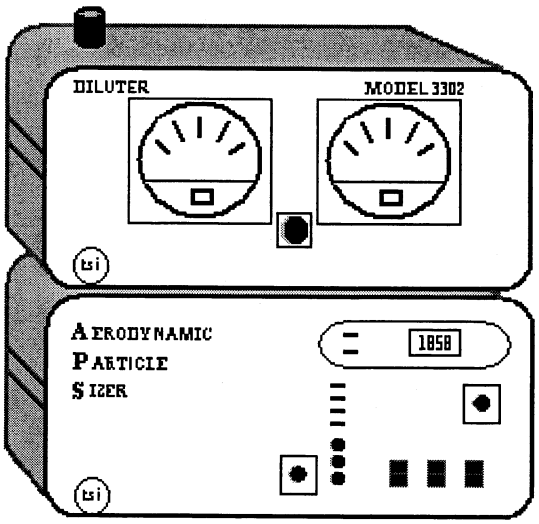


TABLE 1
Summary of Gestation Clinical Findings

**Summary of Gestation Clinical Findings**[+]

**Table 1**

| Observation | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| **Number of Animals Alive at Start of Interval** | 26 | 26 | 26 | 26 |
| **External Appearance** | | | | |
| Material around eyes, Black, Eye/left | 1/1 | 1/1 | 1/1 | 0/0 |
| Material around eyes, Black, Eye/right | 0/0 | 0/0 | 1/1 | 0/0 |
| Material around eyes, Brown, Eye/left | 3/3 | 1/1 | 6/5 | 4/4 |
| Material around eyes, Brown, Eye/right | 1/1 | 1/1 | 5/4 | 3/3 |
| Material around eyes, Red, Eye/left | 98/21 | 65/14 | 130/21 | 69/15 |
| Material around eyes, Red, Eye/right | 90/19 | 44/14 | 95/18 | 63/15 |
| Material around mouth, Red | 0/0 | 0/0 | 2/1 | 0/0 |
| Material around nose, Black | 0/0 | 0/0 | 2/2 | 1/1 |
| Material around nose, Brown | 1/1 | 0/0 | 0/0 | 1/1 |
| Material around nose, Red | 3/2 | 3/3 | 12/5 | 8/4 |
| **Mass** | | | | |
| Mass 1, Large >or=4 cm, Abdominal region | 0/0 | 0/0 | 4/1 | 0/0 |
| Mass 1, Medium 2-3.9 cm, Abdominal region | 0/0 | 0/0 | 2/1 | 0/0 |
| Mass 1, Small 1-1.9 cm, Abdominal region | 0/0 | 0/0 | 2/1 | 0/0 |
| **Pelage/Skin** | | | | |
| Hair absent, Abdominal region | 0/0 | 2/1 | 0/0 | 0/0 |
| Hair absent, Forelimb/left | 0/0 | 12/1 | 0/0 | 13/1 |
| Hair absent, Forelimb/right | 0/0 | 12/1 | 0/0 | 13/1 |
| Hair absent, Hind limb/left | 0/0 | 0/0 | 0/0 | 3/1 |
| Hair absent, Ventral surface | 0/0 | 0/0 | 0/0 | 10/1 |
| Hair sparse, Abdominal region | 2/1 | 14/1 | 0/0 | 0/0 |
| Hair sparse, Forefoot/left | 31/5 | 2/1 | 3/2 | 17/4 |
| Hair sparse, Forefoot/right | 31/5 | 2/1 | 5/3 | 17/4 |
| Hair sparse, Forelimb/left | 29/4 | 28/3 | 23/3 | 39/4 |

[+]Number of times observed/Total number of animals affected  No statistical analysis performed

**Summary of Gestation Clinical Findings[+]**

**Table 1 Cont.**

| Observation | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| **Pelage/Skin** | | | | |
| Hair sparse, Forelimb/right | 29/4 | 28/3 | 30/4 | 39/4 |
| Hair sparse, Hind limb/left | 0/0 | 0/0 | 0/0 | 1/1 |
| Hair sparse, Thoracic region | 4/1 | 0/0 | 0/0 | 0/0 |
| Hair sparse, Ventral surface | 0/0 | 0/0 | 0/0 | 5/1 |
| Scabbed area, Cervical region | 0/0 | 5/1 | 0/0 | 6/1 |
| Scabbed area, Dorsal surface | 1/1 | 0/0 | 8/1 | 0/0 |

[+]Number of times observed/Total number of animals affected  No statistical analysis performed

TABLE 2
Summary of Gestation Body Weight Values

**Table 2** **Summary of Gestation Body Weight Values***

| Endpoint | Day of Gestation | 0 mg/M$^3$ | | | 2.6 mg/M$^3$ | | | 4.4 mg/M$^3$ | | | 6.3 mg/M$^3$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Body Weight g | | | | | | | | | | | | | |
| | 0 | 233.7 | 14.32 | 25 | 229.3 | 14.51 | 25 | 235.4 | 15.91 | 26 | 238.2 | 15.57 | 25 |
| | 3 | 245.6 | 14.04 | 25 | 242.1 | 16.81 | 25 | 249.7 | 13.81 | 26 | 250.8 | 17.15 | 25 |
| | 6 | 255.3 | 14.21 | 25 | 251.6 | 18.44 | 25 | 257.9 | 13.44 | 26 | 259.6 | 17.55 | 25 |
| | 9 | 266.0 | 15.13 | 25 | 262.2 | 19.06 | 25 | 270.9 | 13.83 | 26 | 270.4 | 17.70 | 25 |
| | 12 | 281.6 | 16.30 | 25 | 277.2 | 19.39 | 25 | 286.5 | 13.69 | 26 | 286.1 | 19.77 | 25 |
| | 15 | 298.0 | 17.84 | 25 | 292.9 | 21.66 | 25 | 302.7 | 14.56 | 26 | 303.7 | 20.12 | 25 |
| | 18 | 330.0 | 23.76 | 25 | 326.5 | 25.41 | 25 | 339.5 | 16.93 | 26 | 338.4 | 22.88 | 25 |
| | 20 | 358.4 | 26.66 | 25 | 352.5 | 29.21 | 25 | 369.3 | 18.34 | 26 | 367.5 | 25.54 | 25 |

N - Number of measures used to calculate mean
SD - Standard Deviation

*No statistical significance observed

TABLE 3
Summary of Gestation Body Weight Change Values

**Table 3** **Summary of Gestation Body Weight Change Values***

| | | 0 mg/M$^3$ | | | 2.6 mg/M$^3$ | | | 4.4 mg/M$^3$ | | | 6.3 mg/M$^3$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Endpoint | Day of Gestation | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Body Weight Change g | | | | | | | | | | | | | |
| | 0-3 | 11.9 | 5.05 | 25 | 12.8 | 6.33 | 25 | 14.3 | 6.88 | 26 | 12.7 | 6.88 | 25 |
| | 3-6 | 9.8 | 4.68 | 25 | 9.5 | 3.81 | 25 | 8.2 | 4.90 | 26 | 8.8 | 3.07 | 25 |
| | 6-9 | 10.6 | 5.48 | 25 | 10.6 | 3.65 | 25 | 13.0 | 4.54 | 26 | 10.8 | 3.96 | 25 |
| | 9-12 | 15.6 | 5.28 | 25 | 15.0 | 5.30 | 25 | 15.6 | 5.10 | 26 | 15.7 | 5.74 | 25 |
| | 12-15 | 16.4 | 6.03 | 25 | 15.7 | 6.24 | 25 | 16.2 | 6.74 | 26 | 17.6 | 5.03 | 25 |
| | 15-18 | 32.0 | 8.74 | 25 | 33.6 | 8.92 | 25 | 36.8 | 7.33 | 26 | 34.7 | 7.30 | 25 |
| | 18-20 | 28.4 | 6.70 | 25 | 26.0 | 8.20 | 25 | 29.8 | 5.23 | 26 | 29.1 | 5.51 | 25 |
| | 0-20 | 124.7 | 18.47 | 25 | 123.2 | 22.75 | 25 | 133.9 | 16.78 | 26 | 129.3 | 18.24 | 25 |

N - Number of measures used to calculate mean
SD - Standard Deviation

*No statistical significance observed

TABLE 4
Summary of Gestation Food Consumption Values

**Table 4** **Summary of Gestation Food Consumption Values**

| Endpoint | Day of Gestation | 0 mg/M$^3$ Mean | SD | N | 2.6 mg/M$^3$ Mean | SD | N | 4.4 mg/M$^3$ Mean | SD | N | 6.3 mg/M$^3$ Mean | SD | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Food Consumption g/animal/day | | | | | | | | | | | | | |
| | 0-3 | 19.5 | 1.69 | 25 | 19.1 | 2.08 | 25 | 20.3 | 1.73 | 26 | 20.5 | 1.90 | 25 |
| | 3-6 | 20.4 | 1.93 | 25 | 20.7 | 1.94 | 25 | 20.7 | 1.87 | 26 | 21.4 | 1.66 | 25 |
| | 6-9 | 20.8 | 1.74 | 25 | 21.3 | 2.87 | 25 | 22.1 | 2.21 | 25 | 21.4 | 1.52 | 25 |
| | 9-12 | 21.9 | 1.95 | 25 | 21.9 | 2.64 | 25 | 22.8 | 5.41 | 26 | 22.9 | 2.08 | 25 |
| | 12-15 | 22.4 | 2.75 | 25 | 22.9 | 2.82 | 25 | 23.5 | 2.27 | 26 | 24.0 | 2.31 | 25 |
| | 15-18 | 23.2 | 3.32 | 25 | 24.3 | 3.37 | 25 | 26.8[b] | 2.64 | 26 | 26.6[b] | 2.33 | 25 |
| | 18-20 | 23.9 | 3.96 | 25 | 24.9 | 3.71 | 25 | 26.9[b] | 2.50 | 26 | 26.8[b] | 2.16 | 25 |
| | 0-20 | 21.6 | 1.68 | 25 | 22.0 | 1.96 | 25 | 23.1[b] | 1.64 | 25 | 23.2[b] | 1.60 | 25 |

N - Number of measures used to calculate mean
SD - Standard Deviation

[b]Significantly different from control; ($p<0.01$)

TABLE 5
Incidence of Macroscopic Observations

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

Incidence of Macroscopic Observations
Terminal Sacrifice: Rat

Table 5

| TISSUE<br>OBSERVATION | Severity | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS EXAMINED | | 26 | 26 | 26 | 26 |
| NUMBER WITHIN NORMAL LIMITS | | 26 | 26 | 25 | 26 |
| All Tissues | | (26) | (26) | (25) | (26) |
| Within normal limits | | 26 | 26 | 25 | 26 |
| Lymph Node, Inguinal | | (0) | (0) | (1) | (0) |
| Not identified | | 0 | 0 | 1 | 0 |
| Skin, Subcutis | | (0) | (0) | (1) | (0) |
| Mass | | 0 | 0 | 1 | 0 |

CODE: ( ) = NUMBER OF ANIMALS EXAMINED

TABLE 6
Summary of Organ Weight Values

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

Table 6 Females: Summary of Organ Weight Values - Terminal Sacrifice

| Parameters Measured | 0 mg/M3 (Control) | | | 2.6 mg/M3 | | | 4.4 mg/M3 | | | 6.3 mg/M3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | S.D. | N | Mean | S.D. | N | Mean | S.D. | N | Mean | S.D. | N |
| Brain g | 1.69 | 0.103 | 25 | 1.74 | 0.100 | 26 | 1.74 | 0.111 | 26 | 1.73 | 0.131 | 26 |
| Lung g | 1.32 | 0.158 | 26 | 1.64[b] | 0.182 | 26 | 1.73[b] | 0.178 | 26 | 1.83[b] | 0.176 | 26 |
| Lung/Brain Weight %x10$^{-1}$ | 7.88 | 0.900 | 25 | 9.47[b] | 1.198 | 26 | 9.95[b] | 1.180 | 26 | 10.62[b] | 1.043 | 26 |

S.D. - Standard Deviation
N - Number of Animals

[b]Significantly different from the control; $p<0.01$

TABLE 7
Incidence of Microscopic Observations

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

Incidence of Microscopic Observations
Terminal Sacrifice: Rat
Female

Table 7

| TISSUE<br>OBSERVATION | Severity | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| NUMBER OF ANIMALS EXAMINED | | 10 | 10 | 10 | 10 |
| NUMBER WITHIN NORMAL LIMITS | | 10 | 0 | 0 | 0 |
| Lung | | (10) | (10) | (10) | (10) |
| Within normal limits | | 10 | 0 | 0 | 0 |
| Hyperplasia, type II cell | | 0 | 5 | 4 | 5 |
| | -minimal | 0 | 2 | 4 | 3 |
| | -mild | 0 | 2 | 0 | 2 |
| | -moderate | 0 | 1 | 0 | 0 |
| Inflammation, acute | | 0 | 7 | 4 | 6 |
| | -minimal | 0 | 4 | 4 | 4 |
| | -mild | 0 | 3 | 0 | 2 |
| Macrophages, pigmented alveolar | | 0 | 10 | 10 | 10 |
| | -minimal | 0 | 2 | 1 | 0 |
| | -mild | 0 | 5 | 9 | 3 |
| | -moderate | 0 | 3 | 0 | 7 |

CODE: ( ) = NUMBER OF ANIMALS EXAMINED

TABLE 8
Summary of Maternal and Developmental Observations at Uterine Examination

**Table 8** **Summary of Maternal and Developmental Observations at Uterine Examination**

| Endpoint | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| No. Females on Study | 26 | 26 | 26 | 26 |
| No. Not Pregnant | 1 | 1 | 0 | 1 |
| No. Pregnant | 25 | 25 | 26 | 25 |
| Pregnancy Index* Percent | 96.2 | 96.2 | 100.0 | 96.2 |
| No. Died Pregnant | 0 | 0 | 0 | 0 |
| No. Abortions | 0 | 0 | 0 | 0 |
| No. Early Deliveries | 0 | 0 | 0 | 0 |
| No. Females with All Resorptions | 0 | 0 | 0 | 0 |
| No. Females with Viable Fetuses Day 20 Gestation | 25 | 25 | 26 | 25 |

No. - Number

*No statistical significance observed

**Table 8 Cont.** **Summary of Maternal and Developmental Observations at Uterine Examination***

| Endpoint | | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| Corpora Lutea | | | | | |
| No. per Animal | Mean | 16.0 | 14.9 | 16.5 | 16.2 |
| | SD | 2.61 | 2.33 | 2.45 | 3.29 |
| | N | 25 | 25 | 26 | 25 |
| Implantation Sites | | | | | |
| No. per Animal | Mean | 14.4 | 13.7 | 14.6 | 14.5 |
| | SD | 3.11 | 3.16 | 1.83 | 2.47 |
| | N | 25 | 25 | 26 | 25 |
| Preimplantation Loss | | | | | |
| % per Animal | Mean | 10.30 | 9.40 | 10.34 | 9.04 |
| | SD | 17.561 | 16.085 | 10.605 | 13.587 |
| | N | 25 | 25 | 26 | 25 |
| Viable Fetuses | | | | | |
| No. per Animal | Mean | 13.8 | 13.2 | 14.1 | 13.5 |
| | SD | 2.98 | 3.08 | 1.93 | 2.77 |
| | N | 25 | 25 | 26 | 25 |
| Fetal Sex Ratio | | | | | |
| % Males per Animal | Mean | 48.9 | 49.8 | 48.9 | 48.0 |
| | SD | 18.55 | 15.85 | 13.26 | 15.85 |
| | N | 25 | 25 | 26 | 25 |

No. - Number
SD - Standard Deviation
N - Number of measures used to calculate mean

*No statistical significance observed

**Table 8 Cont.** **Summary of Maternal and Developmental Observations at Uterine Examination***

| Endpoint | | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| Postimplantation Loss | | | | | |
| % Implants per Animal | Mean | 3.36 | 3.59 | 3.47 | 7.11 |
| | SD | 5.448 | 5.360 | 5.552 | 8.611 |
| | N | 25 | 25 | 26 | 25 |
| Nonviable Fetuses | | | | | |
| No. per Animal | Mean | 0.0 | 0.0 | 0.0 | 0.0 |
| | SD | 0.00 | 0.00 | 0.00 | 0.00 |
| | N | 25 | 25 | 26 | 25 |
| Litter Size | | | | | |
| No. per Animal | Mean | 13.8 | 13.2 | 14.1 | 13.5 |
| | SD | 2.98 | 3.08 | 1.93 | 2.77 |
| | N | 25 | 25 | 26 | 25 |
| Resorptions: Early + Late | | | | | |
| No. per Animal | Mean | 0.5 | 0.5 | 0.5 | 1.0 |
| | SD | 0.82 | 0.77 | 0.76 | 1.19 |
| | N | 25 | 25 | 26 | 25 |
| Resorptions: Early | | | | | |
| No. per Animal | Mean | 0.4 | 0.5 | 0.4 | 1.0 |
| | SD | 0.82 | 0.77 | 0.76 | 1.17 |
| | N | 25 | 25 | 26 | 25 |
| Resorptions: Late | | | | | |
| No. per Animal | Mean | 0.1 | 0.0 | 0.1 | 0.0 |
| | SD | 0.28 | 0.00 | 0.27 | 0.20 |
| | N | 25 | 25 | 26 | 25 |

No. - Number
SD - Standard Deviation
N - Number of measures used to calculate mean

*No statistical significance observed

TABLE 9
Summary of Gravid Uterine Weight and
Adjusted Body Weight/Body Weight Change Values

**Table 9** **Summary of Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values***

| | 0 mg/M$^3$ | | | 2.6 mg/M$^3$ | | | 4.4 mg/M$^3$ | | | 6.3 mg/M$^3$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Endpoint | Mean | SD | N | Mean | SD | N | Mean | SD | N | Mean | SD | N |
| Gravid Uterine Weight, g | 75.7 | 15.87 | 25 | 72.6 | 16.35 | 25 | 78.3 | 10.86 | 26 | 75.7 | 13.50 | 25 |
| Final Body Weight, g | 358.4 | 26.66 | 25 | 352.5 | 29.21 | 25 | 369.3 | 18.34 | 26 | 367.5 | 25.54 | 25 |
| Adjusted Final Body Weight, g | 282.6 | 15.80 | 25 | 279.8 | 19.77 | 25 | 291.0 | 14.90 | 26 | 291.8 | 16.72 | 25 |
| Weight Change from Day 0, g | 124.7 | 18.47 | 25 | 123.2 | 22.75 | 25 | 133.9 | 16.78 | 26 | 129.3 | 18.24 | 25 |
| Adjusted Weight Change from Day 0, g | 49.0 | 11.78 | 25 | 50.5 | 11.55 | 25 | 55.7 | 13.03 | 26 | 53.6 | 9.33 | 25 |

N - Number of measures used to calculate mean
SD - Standard Deviation

*No statistical significance observed

TABLE 10
Summary of Fetal Body Weight Values

**Table 10** **Summary of Fetal Body Weight Values*, g**

| | | | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|---|
| Fetal Weight | | | | | | |
| | Males | Mean | 3.72 (3.73) | 3.81 (3.80) | 3.80 (3.80) | 3.85 (3.85) |
| | | SD | 0.262 | 0.299 | 0.256 | 0.361 |
| | | N | 24 | 25 | 26 | 25 |
| | Females | Mean | 3.64 (3.64) | 3.60 (3.60) | 3.55 (3.55) | 3.67 (3.67) |
| | | SD | 0.682 | 0.233 | 0.197 | 0.318 |
| | | N | 25 | 25 | 26 | 25 |
| | Males + Females | Mean | 3.74 (3.74) | 3.70 (3.70) | 3.67 (3.67) | 3.76 (3.76) |
| | | SD | 0.661 | 0.249 | 0.222 | 0.326 |
| | | N | 25 | 25 | 26 | 25 |

SD - Standard Deviation
N - Number of measures used to calculate mean
( ) - Least square mean
* No statistical significance observed

TABLE 11
Summary of Fetal Crown Rump Distance Values

**Table 11** **Summary of Fetal Crown Rump Distance Values*, mm**

| | | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| Fetal Crown Rump Distance, mm | | | | | |
| Males | Mean | 35.6 | 35.9 | 35.9 | 36.0 |
| | SD | 1.52 | 1.43 | 1.58 | 1.79 |
| | N | 24 | 25 | 26 | 25 |
| Females | Mean | 35.4 | 35.3 | 35.3 | 35.3 |
| | SD | 2.62 | 1.18 | 1.38 | 1.58 |
| | N | 25 | 25 | 26 | 25 |
| Males + Females | Mean | 35.7 | 35.6 | 35.6 | 35.6 |
| | SD | 2.52 | 1.18 | 1.41 | 1.61 |
| | N | 25 | 25 | 26 | 25 |

SD - Standard Deviation
N - Number of measures used to calculate mean

* No statistical significance observed

TABLE 12
Summary of Individual Fetal Visceral Observations

**Table 12** **Summary of Individual Fetal Visceral Observations***

| Observation | Classification | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| No. Litters Evaluated | | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | | 173 | 165 | 184 | 170 |
| **Head** | | | | | |
| Eye(s), anophthalmia | M | | | | |
| No. Litters (%) | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| No. Fetuses (%)[1] | | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) |

No.-Number
M- Malformation

[1]Not statistically analyzed

*No statistical significance observed

TABLE 13
Summary of Individual Fetal Skeletal Observations

**Table 13** **Summary of Individual Fetal Skeletal Observations**

| Observation | Classification | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| No. Litters Evaluated | | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | | 173 | 164 | 183 | 167 |
| **Forelimb(s)** | | | | | |
| Metacarpals, not ossified | V | | | | |
| No. Litters (%) | | 9 (36.0) | 9 (36.0) | 2 (7.7)[a] | 8 (32.0) |
| No. Fetuses (%)[1] | | 21 (12.1) | 18 (11.0) | 2 (1.1) | 17 (10.2) |
| **Rib(s)** | | | | | |
| Rib(s), rudimentary | V | | | | |
| No. Litters (%) | | 3 (12.0) | 8 (32.0) | 5 (19.2) | 4 (16.0) |
| No. Fetuses (%)[1] | | 4 (2.3) | 13 (7.9) | 8 (4.4) | 6 (3.6) |
| Rib(s), unilateral full rib | V | | | | |
| No. Litters (%) | | 1 (4.0) | 1 (4.0) | 2 (7.7) | 1 (4.0) |
| No. Fetuses (%)[1] | | 1 (0.6) | 1 (0.6) | 2 (1.1) | 1 (0.6) |
| **Skull** | | | | | |
| Frontal bone, incompletely ossified | V | | | | |
| No. Litters (%) | | 0 (0.0) | 1 (4.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%)[1] | | 0 (0.0) | 1 (0.6) | 0 (0.0) | 0 (0.0) |

No.-Number
V- Variation

[1]Not statistically analyzed

[a]Significantly different from control; ($p<0.05$)

**Table 13 Cont.** **Summary of Individual Fetal Skeletal Observations***

| Observation | Classification | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|---|
| No. Litters Evaluated | | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | | 173 | 164 | 183 | 167 |
| **Skull (cont.)** | | | | | |
| Hyoid, not ossified | V | | | | |
| No. Litters (%) | | 10 (40.0) | 10 (40.0) | 8 (30.8) | 12 (48.0) |
| No. Fetuses (%)[1] | | 16 (9.2) | 27 (16.5) | 13 (7.1) | 37 (22.2) |
| Interparietal bone, incompletely ossified | V | | | | |
| No. Litters (%) | | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (4.0) |
| No. Fetuses (%)[1] | | 0 (0.0) | 1 (0.6) | 0 (0.0) | 1 (0.6) |
| **Sternum** | | | | | |
| Sternebra(e), misaligned | V | | | | |
| No. Litters (%) | | 3 (12.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%)[1] | | 3 (1.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Sternebra(e), not ossified | V | | | | |
| No. Litters (%) | | 14 (56.0) | 16 (64.0) | 18 (69.2) | 18 (72.0) |
| No. Fetuses (%)[1] | | 56 (32.4) | 41 (25.0) | 44 (24.0) | 48 (28.7) |

No.-Number
V- Variation

[1]Not statistically analyzed

*No statistical significance observed

TABLE 14
Summary of External Malformations and Developmental Variations

**Table 14** **Summary of External Malformations and Developmental Variations**

| | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| No. Litters Evaluated | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | 346 | 329 | 367 | 335 |
| **Total Malformations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Total Variations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

No.- Number

No statistical analysis performed

TABLE 15
Summary of Visceral Malformations and Developmental Variations

**Table 15** **Summary of Visceral Malformations and Developmental Variations***

| | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| No. Litters Evaluated | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | 173 | 165 | 184 | 170 |
| **Total Malformations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| No. Fetuses (%)[1] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.6) |
| **Total Variations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%)[1] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

No.- Number [1]Not statistically analyzed *No statistical significance observed

TABLE 16
Summary of Skeletal Malformations and Developmental Variations

**Table 16** **Summary of Skeletal Malformations and Developmental Variations***

| | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| No. Litters Evaluated | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | 173 | 164 | 183 | 167 |
| **Total Malformations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| No. Fetuses (%)[1] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| **Total Variations** | | | | |
| No. Litters (%) | 20 (80.0) | 21 (84.0) | 23 (88.5) | 21 (84.0) |
| No. Fetuses (%)[1] | 72 (41.6) | 70 (42.7) | 58 (31.7) | 75 (44.9) |

No.- Number [1]Not statistically analyzed *No statistical significance observed

TABLE 17
Summary of External, Visceral, and Skeletal Malformations

**Table 17** **Summary of External, Visceral, and Skeletal Malformations***

| | 0 mg/M$^3$ | 2.6 mg/M$^3$ | 4.4 mg/M$^3$ | 6.3 mg/M$^3$ |
|---|---|---|---|---|
| No. Litters Evaluated | 25 | 25 | 26 | 25 |
| No. Fetuses Evaluated | 346 | 329 | 367 | 337 |
| **Total Malformations** | | | | |
| No. Litters (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.0) |
| No. Fetuses (%)[1] | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (0.3) |

No.- Number [1]Not statistically analyzed *No statistical significance observed

# APPENDIX A
Test Article Information and
Diet and Water Sample Analytical Report

## Test Article Information

| | |
|---|---|
| Date Received: | April 5, 2002 |
| Amount Received: | 1 kg |
| Label Identification: | Antimony Trioxide "Antiox" White Star N |
| Lot Number: | 16598 |
| Physical Characteristics: | White powder |
| Expiration Date: | Stable for study duration |
| Storage: | Room temperature |
| TMC Number: | 15562 |

# CERTIFICATE OF ANALYSIS

Inspection certificate DIN 50049/3.1.B ( EN 10204/3.1.B)

## CONTRACT INFORMATION

Customer:
Contract No:
Quality: Antiox "White Star N"
Article No: 080106
Batch No: 16598
Weight: 1kg

## TEST RESULTS

These values have been taken from measurements made on a production run where this batch is a part of.

| Parameter | Unit | Testmethod | Min. | Max. | Actual |
|---|---|---|---|---|---|
| Total Sb2O3 | % | Internal | 99,80 | | 99,87 |
| Pb | ppm | ICP-OES/XRF | 0 | 800 | 596 |
| As | ppm | ICP-OES/XRF | 0 | 800 | 356 |
| Fe | ppm | ICP-OES/XRF | 0 | 20 | 13 |
| Average particle size | µm | Fisher | 0,70 | 1,00 | 0,72 |
| Sieve refusal 45 µm | % | ISO 787-7 | 0,000 | 0,010 | 0,001 |
| Conductivity | µS | DIN 787 XIV | 0 | 10 | 2 |
| Cl | ppm | Internal | 0 | 25 | 10 |
| Na | ppm | Internal | 0 | 15 | 4 |
| volatiles | % | ISO 787-2 | 0 | 0,10 | 0,003 |

We certify that this product conforms to the relevant Campine product specifications: Rev.02/09-03-2001

2/04/2002

Freddy Smans
quality assurance supervisor

Doc 10.5-4-03.A

**chemical solutions ltd.**
*trace elemental analysis*

# ANALYTICAL REPORT

March 27, 2003

Mr. Andrew Terpstra
MPI Research
54943 North Main Street
Mattawan, MI 49071


Sample No. 03031141-2

Client : MPI
Client # : M7473
Description : See below
Sample Type : Misc.
Collector : Client

Study # : 952-002
Date Sampled :
Date Received : 03/24/03
Date Completed: 03/26/03
Return Date : 04/10/03

**03031141** **Food Sample**

| Parameter | Result | Units | PQL | Method | Date | Analyst |
|---|---|---|---|---|---|---|
| Antimony | <0.5 | µg/g | 0.5 | ICP-MS | 03/26/03 | JP |

**03031142** **Water Sample**

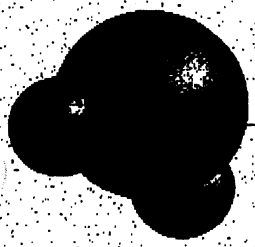
| Parameter | Result | Units | PQL | Method | Date | Analyst |
|---|---|---|---|---|---|---|
| Antimony | <0.002 | µg/g | 0.002 | ICP-MS | 03/26/03 | JP |

Results are reported on an "as received" basis.

Respectfully Submitted,
Chemical Solutions, Ltd.
Ian Milnes/Bg 3/27/03
Ian Milnes
President



273 mulberry drive, suite 9 mechanicsburg, pa 17050 phone 717/697-7536 fax 717/697-4800



# chemical solutions ltd.

*trace elemental analysis*

**CURRENT GOOD LABORATORY PRACTICES**
**CERTIFICATION STATEMENT**

May 20, 2003

Mr. Andrew Terpstra
MPI Research
54946 North Main Street
Mattawan, MI 49071

Dear Mr. Terpstra:

Chemical Solutions Ltd. hereby certifies that the methods used in and the facilities and controls used for the analyses performed on behalf of MPI Research are in compliance with the current Good Manufacturing Practices set forth in the Code of Federal Regulations, Title 21, Parts 210 and 211.

Chemical Solutions Ltd. is registered with the FDA; the registration number is 2531447. The FDA inspected Chemical Solutions in September 2002.

Ronald Andrae
Quality Assurance Officer

5/20/03
Date

273 mulberry drive, suite 9 mechanicsburg, pa 17050 phone 717/697-7536 fax 717/697-4800

# APPENDIX B
Inhalation Data

# 952-002 Group 1 Exposure Summary

| Exposure Date | Exposure Concentration ($mg/m^3$)* | Temperature (°C) | | Percent Relative Humidity | |
|---|---|---|---|---|---|
| | | Mean | S.D. | Mean | S.D. |
| 2/25/03 | NA | 19 | 0.4 | 2 | 2.0 |
| 2/26/03 | NA | 20 | 0.7 | 5 | 0.6 |
| 2/27/03 | NA | 19 | 0.3 | 4 | 0.5 |
| 2/28/03 | NA | 21 | 0.8 | 6 | 0.7 |
| 3/1/03 | NA | 21 | 0.9 | 6 | 0.7 |
| 3/2/03 | NA | 22 | 0.6 | 5 | 1.0 |
| 3/3/03 | NA | 22 | 0.9 | 7 | 1.6 |
| 3/4/03 | NA | 22 | 0.6 | 8 | 1.7 |
| 3/5/03 | NA | 23 | 0.7 | 8 | 2.0 |
| 3/6/03 | NA | 22 | 0.6 | 7 | 1.8 |
| 3/7/03 | NA | 22 | 0.6 | 7 | 1.9 |
| 3/8/03 | NA | 22 | 0.6 | 7 | 2.4 |
| 3/9/03 | NA | 22 | 0.8 | 9 | 3.9 |
| 3/10/03 | NA | 22 | 0.9 | 14 | 5.9 |
| 3/11/03 | NA | 22 | 0.6 | 8 | 2.0 |
| 3/12/03 | NA | 22 | 0.4 | 7 | 1.7 |
| 3/13/03 | NA | 23 | 0.9 | 8 | 2.2 |
| 3/14/03 | NA | 22 | 0.7 | 7 | 2.2 |
| 3/15/03 | NA | 22 | 1.0 | 9 | 1.7 |
| 3/16/03 | NA | 23 | 0.7 | 8 | 1.4 |
| 3/17/03 | NA | 23 | 0.7 | 7 | 1.2 |
| 3/18/03 | NA | 22 | 0.4 | 7 | 0.8 |
| 3/19/03 | NA | 22 | 0.7 | 6 | 0.8 |
| 3/20/03 | NA | 21 | 0.6 | 6 | 0.8 |
| 3/21/03 | NA | 21 | 0.7 | 6 | 0.5 |
| 3/22/03 | NA | 19 | 0.0 | 5 | 0.0 |
| 3/23/03 | NA | 19 | 0.3 | 5 | 0.0 |
| Mean | NA | 21 | | 7 | |
| S.D. | NA | 1.3 | | 2.1 | |

*Compressed air was generated inside the exposure chamber

# 952-002 Group 2 Exposure Summary

| Exposure Date | Nominal Concentration ($mg/m^3$) | Exposure Concentration ($mg/m^3$) | | | | | | Particle Size | | Temperature (°C) | | Percent Relative Humidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.D. | Sample 1 | Sample 2 | Sample 3 | Sample 4 | MMAD (μM) | GSD | Mean | S.D. | Mean | S.D. |
| 2/25/03 | 28.6 | 4.7 | 2.57 | 6.5 | 0.9 | 5.1 | 6.1 | 1.58 | 1.625 | 19 | 0.6 | 3 | 0.5 |
| 2/26/03 | 36.1 | 1.8 | 1.56 | 4.0 | 1.6 | 0.8 | 0.6 | 1.67 | 1.647 | 21 | 0.8 | 3 | 0.3 |
| 2/27/03 | 28.4 | 1.9 | 1.92 | 0.0 | 0.5 | 3.1 | 3.9 | 1.88 | 1.727 | 20 | 0.7 | 3 | 0.0 |
| 2/28/03 | 18.7 | 0.2 | 0.35 | 0.0 | 0.7 | 0.0 | 0.0 | 2.18 | 2.307 | 21 | 0.4 | 3 | 0.0 |
| 3/1/03 | 141.5 | 2.7 | 2.39 | 3.9 | 0.0 | 5.3 | 1.4 | 1.43 | 1.568 | 22 | 0.4 | 3 | 0.0 |
| 3/2/03 | 188.1 | 2.3 | 2.56 | 0.0 | 0.3 | 3.9 | 5.1 | 1.87 | 1.477 | 22 | 0.3 | 3 | 0.0 |
| 3/3/03 | 115.1 | 2.3 | 0.91 | 1.3 | 1.7 | 2.7 | 3.3 | 1.65 | 1.656 | 22 | 0.3 | 3 | 0.6 |
| 3/4/03 | 45.6 | 3.6 | 1.44 | 5.1 | 2.0 | 2.7 | 4.4 | 1.78 | 2.905 | 23 | 0.7 | 2 | 0.5 |
| 3/5/03 | 40.8 | 4.5 | 1.96 | 6.3 | 5.2 | 4.6 | 1.7 | 1.46 | 1.608 | 23 | 0.7 | 2 | 0.5 |
| 3/6/03 | 49.9 | 1.7 | 1.14 | 2.9 | 0.2 | 2.1 | 1.5 | 1.54 | 1.655 | 23 | 0.7 | 2 | 0.5 |
| 3/7/03 | 64.2 | 4.7 | 0.62 | 4.2 | 5.1 | 5.4 | 4.2 | 1.50 | 1.554 | 23 | 0.7 | 2 | 0.5 |
| 3/8/03 | 33.9 | 2.3 | 1.77 | 4.1 | 1.8 | 3.1 | 0.0 | 1.70 | 1.592 | 23 | 0.7 | 3 | 0.3 |
| 3/9/03 | 50.8 | 2.1 | 0.42 | 1.7 | 2.7 | 2.0 | 2.0 | 2.12 | 2.498 | 23 | 0.6 | 2 | 0.5 |
| 3/10/03 | 65.4 | 1.9 | 2.03 | 0.0 | 3.8 | 0.3 | 3.5 | 1.56 | 1.609 | 23 | 0.7 | 3 | 0.7 |
| 3/11/03 | 35.9 | 2.5 | 2.16 | 5.4 | 2.0 | 2.4 | 0.2 | 1.51 | 1.646 | 23 | 0.7 | 2 | 0.5 |
| 3/12/03 | 43.0 | 2.7 | 1.45 | 3.8 | 0.6 | 3.5 | 2.9 | 1.56 | 1.725 | 23 | 0.6 | 2 | 0.4 |
| 3/13/03 | 26.0 | 2.3 | 2.56 | 0.0 | 2.8 | 0.7 | 5.7 | 3.06 | 1.633 | 23 | 0.6 | 3 | 0.5 |
| 3/14/03 | 35.4 | 0.6 | 0.81 | 0.0 | 0.5 | 0.2 | 1.8 | 1.47 | 1.603 | 23 | 0.7 | 3 | 0.3 |
| 3/15/03 | 96.5 | 4.7 | 2.01 | 7.5 | 3.4 | 3.1 | 4.9 | 1.39 | 1.634 | 23 | 0.6 | 3 | 0.0 |
| 3/16/03 | 30.0 | 1.2 | 1.66 | 0.7 | 0.0 | 0.3 | 3.6 | 2.60 | 1.738 | 23 | 0.8 | 3 | 0.0 |
| 3/17/03 | 96.8 | 6.0 | 5.78 | 3.1 | 0.0 | 13.3 | 7.6 | 2.42 | 1.617 | 23 | 0.7 | 3 | 0.0 |
| 3/18/03 | 32.4 | 2.7 | 3.07 | 0.1 | 0.0 | 5.0 | 5.7 | 1.40 | 1.546 | 23 | 0.4 | 3 | 0.0 |
| 3/19/03 | 28.7 | 0.6 | 0.77 | 1.7 | 0.2 | 0.1 | 0.2 | 1.67 | 1.872 | 22 | 0.4 | 3 | 0.0 |
| 3/20/03 | 28.9 | 3.1 | 3.80 | 0.0 | 4.2 | 8.0 | 0.2 | 1.46 | 1.622 | 22 | 0.5 | 3 | 0.0 |
| 3/21/03 | 30.2 | 2.8 | 3.92 | 8.4 | 0.2 | 2.5 | 0.0 | 1.49 | 1.616 | 22 | 0.4 | 3 | 0.4 |
| 3/22/03 | 38.1 | 2.0 | 1.51 | 3.4 | 1.2 | 3.0 | 0.2 | 1.61 | 1.776 | 20 | 0.4 | 3 | 0.5 |
| 3/23/03 | 37.4 | 2.6 | 2.77 | 0.0 | 1.7 | 2.1 | 6.5 | 1.52 | 1.620 | 19 | 0.5 | 4 | 0.0 |
| Mean | 54.3 | * 2.6 | | | | | | 1.74 | 1.744 | 22 | | 3 | |
| S.D. | 40.08 | * 2.43 | | | | | | 0.405 | 0.3189 | 1.3 | | 0.5 | |

* Indicates the calculation of the mean and standard deviation using all of the individual samples.

# 952-002 Group 3 Exposure Summary

| Exposure Date | Nominal Concentration ($mg/m^3$) | Exposure Concentration ($mg/m^3$) | | | | | | Particle Size | | Temperature (°C) | | Percent Relative Humidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.D. | Sample 1 | Sample 2 | Sample 3 | Sample 4 | MMAD (µM) | GSD | Mean | S.D. | Mean | S.D. |
| 2/25/03 | 95.0 | 3.0 | 2.68 | 4.6 | 0.9 | 0.5 | 5.9 | 2.30 | 1.615 | 18 | 0.4 | 5 | 0.9 |
| 2/26/03 | 29.0 | 4.5 | 5.23 | 6.9 | 10.7 | 0.3 | 0.0 | 1.65 | 1.580 | 19 | 0.3 | 4 | 0.5 |
| 2/27/03 | 12.7 | 3.6 | 3.33 | 0.0 | 2.1 | 4.7 | 7.7 | 2.01 | 1.629 | 19 | 0.3 | 5 | 1.2 |
| 2/28/03 | 34.5 | 4.8 | 4.96 | 0.0 | 11.7 | 4.3 | 3.1 | 1.64 | 1.639 | 21 | 0.6 | 6 | 0.7 |
| 3/1/03 | 88.8 | 8.3 | 5.50 | 9.0 | 10.6 | 13.2 | 0.5 | 1.62 | 1.622 | 22 | 0.6 | 5 | 1.1 |
| 3/2/03 | 62.5 | 9.6 | 6.66 | 19.1 | 3.7 | 8.3 | 7.1 | 1.60 | 1.668 | 22 | 0.7 | 5 | 1.2 |
| 3/3/03 | 51.1 | 3.3 | 3.22 | 5.4 | 0.7 | 6.6 | 0.3 | 1.63 | 1.609 | 22 | 0.6 | 7 | 0.9 |
| 3/4/03 | 17.4 | 2.6 | 0.62 | 3.3 | 3.0 | 2.1 | 2.1 | 1.74 | 1.690 | 22 | 0.6 | 7 | 1.1 |
| 3/5/03 | 44.4 | 3.0 | 2.73 | 6.9 | 1.5 | 0.8 | 2.8 | 1.60 | 1.603 | 22 | 0.6 | 8 | 2.1 |
| 3/6/03 | 27.9 | 3.4 | 1.95 | 0.5 | 4.8 | 4.3 | 3.9 | 1.59 | 1.607 | 23 | 0.7 | 6 | 0.9 |
| 3/7/03 | 25.5 | 5.2 | 4.92 | 0.2 | 9.1 | 9.7 | 1.7 | 2.35 | 1.592 | 22 | 0.6 | 6 | 1.0 |
| 3/8/03 | 43.7 | 5.7 | 4.40 | 6.9 | 10.6 | 5.2 | 0.0 | 1.98 | 3.371 | 22 | 0.8 | 6 | 1.3 |
| 3/9/03 | 35.1 | 5.7 | 7.14 | 0.0 | 14.8 | 8.0 | 0.0 | 1.53 | 1.638 | 22 | 0.0 | 5 | 0.0 |
| 3/10/03 | 20.3 | 2.4 | 2.71 | 0.0 | 0.8 | 2.6 | 6.1 | 2.36 | 1.027 | 22 | 0.6 | 7 | 1.1 |
| 3/11/03 | 50.1 | 4.9 | 3.53 | 8.6 | 0.1 | 5.4 | 5.6 | 1.59 | 1.661 | 22 | 0.6 | 7 | 1.0 |
| 3/12/03 | 28.2 | 3.5 | 1.84 | 4.7 | 2.0 | 1.8 | 5.4 | 1.63 | 1.706 | 23 | 0.6 | 6 | 0.9 |
| 3/13/03 | 17.3 | 2.4 | 0.78 | 3.5 | 2.1 | 2.2 | 1.7 | 1.75 | 1.851 | 23 | 0.6 | 4 | 0.4 |
| 3/14/03 | 92.6 | 4.2 | 3.59 | 7.5 | 6.9 | 2.5 | 0.0 | 1.71 | 1.618 | 23 | 0.6 | 4 | 0.6 |
| 3/15/03 | 17.8 | 1.8 | 1.76 | 0.0 | 3.5 | 0.5 | 3.0 | 4.45 | 2.233 | 23 | 0.6 | 4 | 0.7 |
| 3/16/03 | 89.1 | 8.1 | 3.52 | 3.9 | 7.3 | 8.8 | 12.4 | 1.62 | 1.625 | 24 | 0.7 | 4 | 0.4 |
| 3/17/03 | 31.1 | 2.8 | 1.97 | 3.3 | 3.4 | 0.0 | 4.6 | 1.53 | 1.635 | 24 | 0.7 | 3 | 0.4 |
| 3/18/03 | 6.6 | 1.4 | 2.18 | 0.4 | 0.3 | 0.3 | 4.7 | 1.60 | 1.895 | 23 | 0.6 | 3 | 0.5 |
| 3/19/03 | 34.0 | 2.6 | 1.52 | 3.2 | 3.5 | 3.3 | 0.3 | 1.57 | 1.601 | 22 | 0.3 | 3 | 0.5 |
| 3/20/03 | 37.1 | 6.5 | 4.42 | 9.4 | 6.9 | 9.5 | 0.1 | 1.50 | 1.588 | 22 | 0.7 | 3 | 0.5 |
| 3/21/03 | 42.5 | 6.1 | 4.29 | 9.4 | 9.0 | 6.0 | 0.1 | 1.53 | 1.637 | 21 | 0.3 | 4 | 0.0 |
| 3/22/03 | 23.6 | 3.2 | 1.83 | 5.0 | 4.5 | 1.5 | 1.7 | 1.58 | 1.675 | 20 | 0.5 | 4 | 0.0 |
| 3/23/03 | 23.9 | 5.6 | 4.80 | 11.5 | 6.6 | 4.2 | 0.0 | 1.59 | 1.627 | 19 | 0.3 | 5 | 0.5 |
| Mean | 40.1 | * 4.4 | | | | | | 1.82 | 1.713 | 22 | | 5 | |
| S.D. | 25.15 | * 3.88 | | | | | | 0.582 | 0.3780 | 1.5 | | 1.4 | |

* Indicates the calculation of the mean and standard deviation using all of the individual samples.

# 952-002 Group 4 Exposure Summary

| Exposure Date | Nominal Concentration ($mg/m^3$) | Exposure Concentration ($mg/m^3$) | | | | | | Particle Size | | Temperature (°C) | | Percent Relative Humidity | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Mean | S.D. | Sample 1 | Sample 2 | Sample 3 | Sample 4 | MMAD (µM) | GSD | Mean | S.D. | Mean | S.D. |
| 2/25/03 | 61.4 | 8.2 | 8.43 | 20.4 | 6.2 | 4.8 | 1.2 | 1.53 | 1.597 | 18 | 0.4 | 5 | 0.5 |
| 2/26/03 | 61.5 | 6.9 | 1.43 | 7.8 | 5.1 | 8.3 | 6.5 | 1.70 | 1.837 | 19 | 0.4 | 4 | 0.3 |
| 2/27/03 | 21.2 | 5.2 | 5.25 | 0.0 | 1.4 | 9.1 | 10.3 | 1.85 | 1.770 | 19 | 0.4 | 3 | 0.5 |
| 2/28/03 | 48.0 | 8.8 | 3.45 | 5.4 | 6.2 | 11.6 | 11.9 | 1.59 | 1.664 | 20 | 0.4 | 4 | 0.0 |
| 3/1/03 | 50.8 | 9.9 | 6.71 | 12.5 | 9.7 | 0.7 | 16.5 | 1.48 | 1.599 | 21 | 0.3 | 3 | 0.4 |
| 3/2/03 | 131.7 | 2.6 | 3.26 | 7.1 | 0.0 | 0.4 | 2.8 | 1.42 | 1.601 | 21 | 0.6 | 3 | 0.3 |
| 3/3/03 | 81.6 | 7.7 | 1.26 | 9.4 | 6.9 | 7.9 | 6.6 | 1.55 | 1.638 | 21 | 0.6 | 3 | 0.4 |
| 3/4/03 | 39.4 | 6.1 | 3.81 | 11.3 | 3.0 | 3.5 | 6.6 | 1.49 | 1.586 | 22 | 0.9 | 3 | 0.3 |
| 3/5/03 | 40.9 | 6.7 | 3.09 | 10.4 | 4.2 | 4.1 | 8.1 | 1.57 | 1.689 | 22 | 0.6 | 3 | 0.3 |
| 3/6/03 | 55.7 | 8.5 | 4.49 | 11.7 | 1.9 | 10.9 | 9.4 | 1.46 | 1.558 | 22 | 0.6 | 3 | 0.3 |
| 3/7/03 | 56.1 | 7.1 | 6.23 | 5.1 | 16.1 | 5.3 | 1.8 | 1.58 | 1.675 | 22 | 0.7 | 3 | 0.3 |
| 3/8/03 | 62.1 | 7.2 | 7.16 | 8.7 | 2.7 | 0.8 | 16.7 | 1.83 | 2.503 | 22 | 0.6 | 2 | 0.7 |
| 3/9/03 | 36.3 | 6.1 | 2.08 | 8.8 | 3.8 | 5.5 | 6.4 | 1.57 | 1.726 | 22 | 0.6 | 3 | 0.3 |
| 3/10/03 | 31.2 | 8.2 | 2.23 | 10.1 | 6.0 | 6.5 | 10.1 | 1.54 | 1.584 | 22 | 0.9 | 3 | 0.6 |
| 3/11/03 | 41.9 | 3.6 | 3.56 | 6.4 | 7.0 | 0.6 | 0.5 | 1.54 | 1.645 | 22 | 0.9 | 3 | 0.3 |
| 3/12/03 | 47.6 | 8.3 | 6.74 | 6.7 | 8.6 | 0.7 | 17.0 | 1.55 | 1.672 | 22 | 0.6 | 3 | 0.4 |
| 3/13/03 | 31.7 | 4.4 | 1.19 | 6.1 | 3.4 | 4.3 | 3.8 | 1.50 | 1.681 | 23 | 0.5 | 6 | 0.5 |
| 3/14/03 | 58.5 | 6.2 | 0.71 | 5.6 | 7.1 | 5.7 | 6.5 | 1.87 | 2.441 | 23 | 0.3 | 6 | 0.4 |
| 3/15/03 | 53.5 | 6.2 | 6.91 | 0.3 | 4.3 | 16.2 | 4.0 | 1.57 | 1.793 | 23 | 0.3 | 6 | 0.7 |
| 3/16/03 | 51.4 | 6.0 | 4.16 | 0.9 | 10.4 | 4.5 | 8.1 | 1.51 | 1.676 | 24 | 0.6 | 5 | 0.7 |
| 3/17/03 | 48.4 | 8.2 | 0.74 | 7.5 | 7.7 | 9.0 | 8.7 | 1.49 | 1.620 | 24 | 0.7 | 5 | 0.4 |
| 3/18/03 | 37.3 | 5.5 | 3.54 | 5.5 | 9.0 | 6.7 | 0.6 | 1.49 | 1.588 | 24 | 0.7 | 5 | 0.3 |
| 3/19/03 | 34.3 | 6.1 | 1.22 | 5.5 | 6.8 | 4.7 | 7.4 | 1.51 | 1.610 | 23 | 0.4 | 6 | 0.5 |
| 3/20/03 | 39.9 | 6.5 | 1.53 | 7.7 | 7.8 | 4.6 | 6.0 | 1.48 | 1.693 | 22 | 0.5 | 6 | 0.0 |
| 3/21/03 | 18.8 | 1.1 | 2.07 | 0.2 | 4.2 | 0.0 | 0.0 | 2.08 | 1.378 | 21 | 0.3 | 6 | 0.0 |
| 3/22/03 | 27.0 | 3.9 | 2.68 | 0.1 | 5.4 | 3.8 | 6.1 | 1.61 | 1.794 | 20 | 0.4 | 6 | 0.5 |
| 3/23/03 | 33.5 | 4.7 | 3.95 | 7.1 | 2.7 | 0.1 | 8.7 | 1.60 | 1.652 | 19 | 0.3 | 7 | 0.0 |
| Mean | 48.2 | * 6.3 | | | | | | 1.59 | 1.714 | 22 | | 4 | |
| S.D. | 21.85 | * 4.18 | | | | | | 0.151 | 0.2363 | 1.6 | | 1.5 | |

* Indicates the calculation of the mean and standard deviation using all of the individual samples.

**An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide**

## ANALYTICAL METHOD

### SCOPE

This analytical method was adapted from OSHA methods number ID-121 and modified as necessary for the assay of antimony trioxide ($Sb_2O_3$). Exposure chamber air samples are collected on mixed-cellulose ester filters using a calibrated sampling pump. Samples are digested using mineral acid digestions. Elemental analysis of the prepared sample solutions is performed by atomic absorption (AA).

### EQUIPMENT

1. Varian Spectra AA-5, Atomic Absorption Spectrometer, (Serial No. 94081575)
2. Analytical Balance (Sartorius, Serial No. 60101218)
3. Volumetric flasks, pipettes, beakers
4. Phillips beakers – 125 mL
5. Exhaust hood and hotplate (Thermolyne, Model Cimarec 3)
6. Forceps

### REAGENTS and MATERIALS

1. Deionized water (DI $H_2O$)
2. Hydrochloric acid (HCl), concentrated (37%)
3. Nitric acid ($HNO_3$), concentrated (70%)
4. Atomic absorption standard solution containing approximately 1000µg/mL antimony in 8% wt. HCl (Lot No. 16413DS)
5. Mixed cellulose ester (MCE) filter pads (.045 µm pore size) – 25 mm

### PROCEDURE:

A. Spectroscopic Conditions:

Lamp: Varian antimony hollow cathode lamp
Lamp current: 10 mA
Fuel: acetylene
Support: ultra zero air
Flame stoichiometry: oxidizing
Wavelength: 217.6 nm
Slit width: 0.2 nm
AA parameters adjusted to obtain optimum response.

B. Glassware Preparation

1. Place the Phillips beakers in an exhaust hood and add approximately 8 mL of HCl in each beaker. Heat moderately and decant the acid into a waste container. Allow the beakers to cool before removing from hood. Wash with soap and water, rinse with tap water and a final rinse with DI $H_20$. Rinse all volumetric flasks with 10% HCl. Wash with soap and water and a final rinse with DI $H_20$.

C. Preparation of Standards

1. Commercially available aqueous stock standards are used (Aldrich Chemical Co.)

2. Working standards are prepared by diluting stock standard solutions to the appropriate ranges using 10% HCl as the diluent. The standard concentrations should bracket the expected sample concentrations.

D. Sample Preparation and Analysis

1. Receive the MCE filters in labeled Phillips beakers from the Inhalation exposure area.

2. To digest the MCE filter matrix, treat the sample with approximately 4 to 5 mL concentrated $HNO_3$. Place the beakers on a hotplate and heat the samples until about 1 mL remains. Add a second portion of approximately 1 to 2 mL concentrated $HNO_3$ and repeat the process. Allow the samples to cool to room temperature in an exhaust hood. Add approximately 8 mL of concentrated HCl. Heat gently and swirl to dissolve any remaining antimony (do not boil in HCl since some of the antimony would be lost). Allow the samples to cool to room temperature in an exhaust hood.

3. Quantitatively transfer the solution to a 25 mL volumetric flask and dilute to volume with DI $H_20$.

4. For dilutions: use 10% HCl as the diluent.

5. Aspirate the resulting solution into the AA for analysis.

6. Analyze a blank sample containing only the MCE filter during each sample set using the same procedures described above.

D. Analysis Procedure

1. Prepare standard and sample solutions.
2. Set-up instrument and sampling system as described.
3. Aspirate standards before exposure samples are running.
4. Aspirate all samples.

E. Quantitation:

1. A calibration curve is developed using linear regression analysis (including correlation coefficient) of the working standards concentration and respective absorbance units. Sample values are derived from the regression data.

2. Calculate µg/ml, mg found, and $mg/M^3$ air of antimony trioxide in each sample using the calibration curve, dilution factor, total formulation factor, sample flow rate, and sample time.

F. Calculations:

Total Formulation Factor:

Formula weight of Antimony in compound = 243.5
Formula weight of Oxygen in compound = 47.9982
Total = 291.4982
Decimal fraction of antimony in compound = 0.8353
Reciprocal of 0.8353 = 1.197

$$C = \frac{R-I}{S}$$

$$W = CVF$$

$$A = \frac{W}{L\,T}$$

where:

R = absorbance units of test article
C = concentration from standard curve
S = slope of standard curve
I = y-intercept of standard curve
W= Amount of test article found in µg
V = final analytical volume (dilution factor)
A = concentration of test article in exposure system, $mg/M^3$
(note: 1 $M^3$ = 1000L)
L = flow rate of sampling system, L/min
T = total sampling time, min
F = total formulation factor

# APPENDIX C
Record of Animal Fate and Disposition

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Record of Animal Fate and Disposition - FEMALE**

| Group, Animal Number | Fate | Day |
|---|---|---|
| 0 mg/M$^3$ (Control) | | |
| 301 | Terminal Sacrifice | 20 |
| 302 | Terminal Sacrifice | 20 |
| 303 | Terminal Sacrifice | 20 |
| 304 | Terminal Sacrifice | 20 |
| 305 | Terminal Sacrifice | 20 |
| 306 | Terminal Sacrifice | 20 |
| 307 | Terminal Sacrifice | 20 |
| 308 | Terminal Sacrifice | 20 |
| 309 | Terminal Sacrifice | 20 |
| 310 | Terminal Sacrifice | 20 |
| 311 | Terminal Sacrifice | 20 |
| 312 | Terminal Sacrifice | 20 |
| 313 | Terminal Sacrifice | 20 |
| 314 | Terminal Sacrifice | 20 |
| 315 | Terminal Sacrifice | 20 |
| 316 | Terminal Sacrifice | 20 |
| 317 | Terminal Sacrifice | 20 |
| 318 | Terminal Sacrifice | 20 |
| 319 | Terminal Sacrifice | 20 |
| 320 | Terminal Sacrifice | 20 |
| 321 | Terminal Sacrifice | 20 |
| 322 | Terminal Sacrifice | 20 |
| 323 | Terminal Sacrifice | 20 |
| 324 | Terminal Sacrifice | 20 |
| 325 | Terminal Sacrifice | 20 |
| 326 | Terminal Sacrifice | 20 |
| 2.6 mg/M$^3$ | | |
| 327 | Terminal Sacrifice | 20 |
| 328 | Terminal Sacrifice | 20 |
| 329 | Terminal Sacrifice | 20 |
| 330 | Terminal Sacrifice | 20 |
| 331 | Terminal Sacrifice | 20 |
| 332 | Terminal Sacrifice | 20 |
| 333 | Terminal Sacrifice | 20 |
| 334 | Terminal Sacrifice | 20 |
| 335 | Terminal Sacrifice | 20 |
| 336 | Terminal Sacrifice | 20 |
| 337 | Terminal Sacrifice | 20 |
| 338 | Terminal Sacrifice | 20 |
| 339 | Terminal Sacrifice | 20 |
| 340 | Terminal Sacrifice | 20 |
| 341 | Terminal Sacrifice | 20 |
| 342 | Terminal Sacrifice | 20 |
| 343 | Terminal Sacrifice | 20 |
| 344 | Terminal Sacrifice | 20 |
| 345 | Terminal Sacrifice | 20 |
| 346 | Terminal Sacrifice | 20 |

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Record of Animal Fate and Disposition - FEMALE**

| Group, Animal Number | Fate | Day |
|---|---|---|
| 2.6 mg/M$^3$ | | |
| 347 | Terminal Sacrifice | 20 |
| 348 | Terminal Sacrifice | 20 |
| 349 | Terminal Sacrifice | 20 |
| 350 | Terminal Sacrifice | 20 |
| 351 | Terminal Sacrifice | 20 |
| 352 | Terminal Sacrifice | 20 |
| 4.4 mg/M$^3$ | | |
| 353 | Terminal Sacrifice | 20 |
| 354 | Terminal Sacrifice | 20 |
| 355 | Terminal Sacrifice | 20 |
| 356 | Terminal Sacrifice | 20 |
| 357 | Terminal Sacrifice | 20 |
| 358 | Terminal Sacrifice | 20 |
| 359 | Terminal Sacrifice | 20 |
| 360 | Terminal Sacrifice | 20 |
| 361 | Terminal Sacrifice | 20 |
| 362 | Terminal Sacrifice | 20 |
| 363 | Terminal Sacrifice | 20 |
| 364 | Terminal Sacrifice | 20 |
| 365 | Terminal Sacrifice | 20 |
| 366 | Terminal Sacrifice | 20 |
| 367 | Terminal Sacrifice | 20 |
| 368 | Terminal Sacrifice | 20 |
| 369 | Terminal Sacrifice | 20 |
| 370 | Terminal Sacrifice | 20 |
| 371 | Terminal Sacrifice | 20 |
| 372 | Terminal Sacrifice | 20 |
| 373 | Terminal Sacrifice | 20 |
| 374 | Terminal Sacrifice | 20 |
| 375 | Terminal Sacrifice | 20 |
| 376 | Terminal Sacrifice | 20 |
| 377 | Terminal Sacrifice | 20 |
| 378 | Terminal Sacrifice | 20 |
| 6.3 mg/M$^3$ | | |
| 379 | Terminal Sacrifice | 20 |
| 380 | Terminal Sacrifice | 20 |
| 381 | Terminal Sacrifice | 20 |
| 382 | Terminal Sacrifice | 20 |
| 383 | Terminal Sacrifice | 20 |
| 384 | Terminal Sacrifice | 20 |
| 385 | Terminal Sacrifice | 20 |
| 386 | Terminal Sacrifice | 20 |
| 387 | Terminal Sacrifice | 20 |
| 388 | Terminal Sacrifice | 20 |
| 389 | Terminal Sacrifice | 20 |

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Record of Animal Fate and Disposition - FEMALE**

| Group, Animal Number | Fate | Day |
|---|---|---|
| 6.3 mg/M$^3$ | | |
| 390 | Terminal Sacrifice | 20 |
| 391 | Terminal Sacrifice | 20 |
| 392 | Terminal Sacrifice | 20 |
| 393 | Terminal Sacrifice | 20 |
| 394 | Terminal Sacrifice | 20 |
| 395 | Terminal Sacrifice | 20 |
| 396 | Terminal Sacrifice | 20 |
| 397 | Terminal Sacrifice | 20 |
| 398 | Terminal Sacrifice | 20 |
| 399 | Terminal Sacrifice | 20 |
| 400 | Terminal Sacrifice | 20 |
| 401 | Terminal Sacrifice | 20 |
| 402 | Terminal Sacrifice | 20 |
| 403 | Terminal Sacrifice | 20 |
| 404 | Terminal Sacrifice | 20 |

# APPENDIX D
Individual Gestation Clinical Findings

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 0 mg/M$^3$ | | |
| 301 | No Abnormalities Detected | 0-20 |
| 302 | No Abnormalities Detected | 0-3, 20 |
| | Hair sparse, Forefoot/left | 4-9 |
| | Hair sparse, Forefoot/right | 4-9 |
| | Hair sparse, Forelimb/left | 10-19 |
| | Hair sparse, Forelimb/right | 10-19 |
| | Material around eyes, Red, Eye/left | 12 |
| | Material around eyes, Red, Eye/right | 12 |
| 303 | No Abnormalities Detected | 0-20 |
| 304 | No Abnormalities Detected | 0-10, 20 |
| | Hair sparse, Forefoot/left | 17-18 |
| | Hair sparse, Forefoot/right | 17-18 |
| | Material around eyes, Red, Eye/left | 12-18 |
| | Material around eyes, Red, Eye/right | 11-18 |
| | Material around nose, Red | 18-19 |
| 305 | No Abnormalities Detected | 0-3, 20 |
| | Hair sparse, Forefoot/left | 4-13 |
| | Hair sparse, Forefoot/right | 4-13 |
| | Hair sparse, Forelimb/left | 14-19 |
| | Hair sparse, Forelimb/right | 14-19 |
| | Material around eyes, Red, Eye/left | 18-19 |
| | Material around eyes, Red, Eye/right | 18-19 |
| 306 | No Abnormalities Detected | 0-1, 9-11, 15-17, 20 |
| | Material around eyes, Red, Eye/left | 2-4, 12-14, 18-19 |
| | Material around eyes, Red, Eye/right | 2-8, 12-14, 18-19 |
| 307 | No Abnormalities Detected | 0-4 |
| | Hair sparse, Forefoot/left | 5-8 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 0 mg/M$^3$ | | |
| | Hair sparse, Forefoot/right | 5-8 |
| | Hair sparse, Forelimb/left | 9-20 |
| | Hair sparse, Forelimb/right | 9-20 |
| | Hair sparse, Thoracic region | 17-20 |
| | Material around eyes, Red, Eye/left | 5-7, 19 |
| | Material around eyes, Red, Eye/right | 5-9, 18-19 |
| 308 | No Abnormalities Detected | 0-4, 15-20 |
| | Hair sparse, Forefoot/left | 5-13 |
| | Hair sparse, Forefoot/right | 5-13 |
| | Hair sparse, Forelimb/left | 14 |
| | Hair sparse, Forelimb/right | 14 |
| 309 | No Abnormalities Detected | 0-6, 10, 12-18, 20 |
| | Material around eyes, Red, Eye/left | 7-9, 11 |
| | Material around nose, Red | 19 |
| 310 | No Abnormalities Detected | 0-10, 16-20 |
| | Material around eyes, Black, Eye/left | 14 |
| | Material around eyes, Red, Eye/left | 11-13, 15 |
| | Material around eyes, Red, Eye/right | 11-13 |
| 311 | No Abnormalities Detected | 0-20 |
| 312 | No Abnormalities Detected | 0-8, 17-20 |
| | Material around eyes, Brown, Eye/left | 13 |
| | Material around eyes, Red, Eye/left | 9-12, 14-15 |
| | Material around eyes, Red, Eye/right | 9-12, 16 |
| 313 | No Abnormalities Detected | 0-20 |
| 314 | No Abnormalities Detected | 1-3, 7-9, 12-14, 17-18, 20 |
| | Material around eyes, Red, Eye/left | 4-6, 10-11, 15-16, 19 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 0 mg/M$^3$ | | |
| | Material around eyes, Red, Eye/right | 5-6, 15-16, 19 |
| | Scabbed area, Dorsal surface | 0 |
| 315 | No Abnormalities Detected | 0-2, 9, 11-17, 20 |
| | Material around eyes, Brown, Eye/left | 5 |
| | Material around eyes, Brown, Eye/right | 5 |
| | Material around eyes, Red, Eye/left | 3-4, 6-8, 18-19 |
| | Material around eyes, Red, Eye/right | 3-4, 6-8, 10, 19 |
| 316 | No Abnormalities Detected | 0-8, 12-14, 17-20 |
| | Material around eyes, Red, Eye/left | 9-11, 15-16 |
| | Material around eyes, Red, Eye/right | 11 |
| 317 | No Abnormalities Detected | 0-4, 7-10, 17, 20 |
| | Material around eyes, Red, Eye/left | 5-6, 11-16, 18-19 |
| | Material around eyes, Red, Eye/right | 5-6, 11-15, 18-19 |
| 318 | No Abnormalities Detected | 0-2, 7-9, 11-14, 18-20 |
| | Material around eyes, Brown, Eye/left | 4 |
| | Material around eyes, Red, Eye/left | 3, 5-6, 10, 15-17 |
| | Material around eyes, Red, Eye/right | 3-6, 10, 16-17 |
| 319 | No Abnormalities Detected | 0-4, 6-7, 11-20 |
| | Material around eyes, Red, Eye/left | 5, 8-10 |
| | Material around eyes, Red, Eye/right | 5, 8 |
| 320 | No Abnormalities Detected | 0-7, 10-20 |
| | Material around eyes, Red, Eye/left | 8-9 |
| | Material around eyes, Red, Eye/right | 8-9 |
| 321 | No Abnormalities Detected | 0-12, 15-20 |
| | Material around eyes, Red, Eye/left | 13-14 |
| 322 | No Abnormalities Detected | 0-1, 6, 12-20 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 0 mg/M$^3$ | | |
| | Material around eyes, Red, Eye/left | 2-5, 7-11 |
| | Material around eyes, Red, Eye/right | 2-5, 7-11 |
| 323 | No Abnormalities Detected | 0-1, 3-6, 9-12, 15-18 |
| | Hair sparse, Abdominal region | 19-20 |
| | Material around eyes, Red, Eye/left | 7-8, 14 |
| | Material around eyes, Red, Eye/right | 7-8, 13-14 |
| | Material around nose, Brown | 2 |
| 324 | No Abnormalities Detected | 0-5, 7-13, 15-20 |
| | Material around eyes, Red, Eye/left | 6, 14 |
| | Material around eyes, Red, Eye/right | 6, 14 |
| 325 | No Abnormalities Detected | 0-11, 14-20 |
| | Material around eyes, Red, Eye/left | 12-13 |
| | Material around eyes, Red, Eye/right | 12-13 |
| 326 | No Abnormalities Detected | 0-1, 3-11, 13-20 |
| | Material around eyes, Red, Eye/left | 12 |
| | Material around eyes, Red, Eye/right | 2, 12 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 2.6 mg/M$^3$ | | |
| 327 | No Abnormalities Detected | 0-20 |
| 328 | No Abnormalities Detected | 0-14, 16-20 |
| | Material around eyes, Red, Eye/right | 15 |
| 329 | No Abnormalities Detected | 0-12, 18, 20 |
| | Material around nose, Red | 19 |
| | Scabbed area, Cervical region | 13-17 |
| 330 | No Abnormalities Detected | 0-7, 9-20 |
| | Material around eyes, Red, Eye/left | 8 |
| | Material around eyes, Red, Eye/right | 8 |
| 331 | No Abnormalities Detected | 0-7, 9-20 |
| | Material around eyes, Red, Eye/left | 8 |
| | Material around eyes, Red, Eye/right | 8 |
| 332 | No Abnormalities Detected | 0-20 |
| 333 | No Abnormalities Detected | 0-20 |
| 334 | No Abnormalities Detected | 0-3, 6-7, 9-10, 13-17, 19-20 |
| | Material around eyes, Red, Eye/left | 4-5, 8, 11-12, 18 |
| | Material around eyes, Red, Eye/right | 11-12, 18 |
| 335 | No Abnormalities Detected | 0-20 |
| 336 | No Abnormalities Detected | 0-6, 10-20 |
| | Material around eyes, Red, Eye/left | 7-9 |
| | Material around eyes, Red, Eye/right | 7-9 |
| 337 | No Abnormalities Detected | 0-2, 4-15, 17-20 |
| | Material around eyes, Red, Eye/left | 3 |
| | Material around nose, Red | 16 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 2.6 mg/M$^3$ | | |
| 338 | No Abnormalities Detected | 0-2, 6-16, 18-20 |
| | Material around eyes, Red, Eye/left | 3-5, 17 |
| | Material around eyes, Red, Eye/right | 3-5, 17 |
| 339 | No Abnormalities Detected | 0-20 |
| 340 | No Abnormalities Detected | 0-15, 17-20 |
| | Material around eyes, Red, Eye/right | 16 |
| 341 | No Abnormalities Detected | 0-20 |
| 342 | No Abnormalities Detected | 0-4 |
| | Hair absent, Abdominal region | 19-20 |
| | Hair sparse, Abdominal region | 5-18 |
| | Hair sparse, Forelimb/left | 12-20 |
| | Hair sparse, Forelimb/right | 12-20 |
| | Material around eyes, Red, Eye/left | 9-10 |
| 343 | No Abnormalities Detected | 20 |
| | Hair absent, Forelimb/left | 4-15 |
| | Hair absent, Forelimb/right | 4-15 |
| | Hair sparse, Forelimb/left | 0-3, 16-19 |
| | Hair sparse, Forelimb/right | 0-3, 16-19 |
| | Material around eyes, Red, Eye/left | 2-3 |
| | Material around eyes, Red, Eye/right | 2-3, 15 |
| 344 | No Abnormalities Detected | 0-20 |
| 345 | No Abnormalities Detected | 0-20 |
| 346 | No Abnormalities Detected | 0, 3-4, 7, 10-13, 15-20 |
| | Material around eyes, Red, Eye/left | 1-2, 5-6, 8-9, 14 |
| | Material around eyes, Red, Eye/right | 1-2, 5-6, 14 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 2.6 mg/M$^3$ | | |
| 347 | No Abnormalities Detected | 0-1, 3, 6-7, 15-20 |
| | Material around eyes, Red, Eye/left | 2, 4-5, 8-13 |
| | Material around eyes, Red, Eye/right | 2, 4-5, 8-13 |
| | Material around nose, Red | 14 |
| 348 | No Abnormalities Detected | 0-2, 9-12, 14-20 |
| | Material around eyes, Red, Eye/left | 3-8, 13 |
| | Material around eyes, Red, Eye/right | 3-4, 13 |
| 349 | No Abnormalities Detected | 0-20 |
| 350 | No Abnormalities Detected | 4-6 |
| | Hair sparse, Forefoot/left | 7-8 |
| | Hair sparse, Forefoot/right | 7-8 |
| | Hair sparse, Forelimb/left | 10-20 |
| | Hair sparse, Forelimb/right | 10-20 |
| | Material around eyes, Brown, Eye/left | 2 |
| | Material around eyes, Brown, Eye/right | 2 |
| | Material around eyes, Red, Eye/left | 0-1, 3, 7-9, 12-13 |
| | Material around eyes, Red, Eye/right | 0-1, 3, 7-9, 12 |
| 351 | No Abnormalities Detected | 0-4, 18-20 |
| | Material around eyes, Black, Eye/left | 9 |
| | Material around eyes, Red, Eye/left | 5-8, 10-17 |
| | Material around eyes, Red, Eye/right | 12, 17 |
| 352 | No Abnormalities Detected | 0, 2-14, 16-20 |
| | Material around eyes, Red, Eye/left | 1, 15 |
| | Material around eyes, Red, Eye/right | 1 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 4.4 mg/M$^3$ | | |
| 353 | No Abnormalities Detected | 0-18, 20 |
| | Material around eyes, Red, Eye/left | 19 |
| 354 | No Abnormalities Detected | 0-2, 6-8, 10-18, 20 |
| | Material around eyes, Red, Eye/left | 3-5, 9, 19 |
| | Material around eyes, Red, Eye/right | 3-5, 19 |
| 355 | No Abnormalities Detected | 0-2, 6, 10-17, 19-20 |
| | Material around eyes, Red, Eye/left | 3-5, 7-8, 18 |
| | Material around eyes, Red, Eye/right | 3-5, 7-8, 18 |
| | Material around nose, Red | 9 |
| 356 | No Abnormalities Detected | 0-4, 7-17, 19-20 |
| | Material around eyes, Red, Eye/right | 18 |
| | Material around nose, Red | 5-6 |
| 357 | No Abnormalities Detected | 0-4, 15-17, 20 |
| | Material around eyes, Red, Eye/left | 5-8, 18-19 |
| | Material around eyes, Red, Eye/right | 8, 18-19 |
| | Material around nose, Red | 5-8 |
| | Scabbed area, Dorsal surface | 7-14 |
| 358 | No Abnormalities Detected | 0-17, 19-20 |
| | Material around eyes, Red, Eye/left | 18 |
| 359 | No Abnormalities Detected | 0-13, 17-20 |
| | Material around nose, Red | 14-16 |
| 360 | No Abnormalities Detected | 0-16, 18-20 |
| | Material around eyes, Red, Eye/right | 17 |
| 361 | No Abnormalities Detected | 0-6, 8-15, 17-20 |
| | Material around eyes, Red, Eye/left | 7, 16 |
| | Material around eyes, Red, Eye/right | 7, 16 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 4.4 mg/M$^3$ | | |
| | Material around nose, Black | 7 |
| 362 | No Abnormalities Detected | 0-3, 6-12 |
| | Mass 1, Large >or=4 cm, Abdominal region | 15-18 |
| | Mass 1, Medium 2-3.9 cm, Abdominal region | 19-20 |
| | Mass 1, Small 1-1.9 cm, Abdominal region | 13-14 |
| | Material around eyes, Red, Eye/left | 17-18 |
| | Material around mouth, Red | 4-5 |
| 363 | No Abnormalities Detected | 0-2, 12-14, 17-18, 20 |
| | Material around eyes, Red, Eye/left | 3-11, 15-16, 19 |
| | Material around eyes, Red, Eye/right | 3-11, 15 |
| 364 | No Abnormalities Detected | 0-2, 6-7, 9-14, 18-20 |
| | Material around eyes, Red, Eye/left | 3-5, 8, 15-17 |
| | Material around eyes, Red, Eye/right | 3-5, 8, 15-17 |
| 365 | No Abnormalities Detected | 0-5, 7-20 |
| | Material around eyes, Red, Eye/left | 6 |
| 366 | No Abnormalities Detected | 0-2, 10-20 |
| | Material around eyes, Red, Eye/left | 3-9 |
| | Material around eyes, Red, Eye/right | 3-9 |
| 367 | No Abnormalities Detected | 0-5, 17-18, 20 |
| | Hair sparse, Forefoot/left | 6 |
| | Hair sparse, Forefoot/right | 6 |
| | Hair sparse, Forelimb/left | 7-16 |
| | Hair sparse, Forelimb/right | 7-16 |
| | Material around eyes, Brown, Eye/left | 13 |
| | Material around eyes, Brown, Eye/right | 13 |
| | Material around eyes, Red, Eye/left | 6-12, 14-15, 19 |
| | Material around eyes, Red, Eye/right | 14-15, 19 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 4.4 mg/M$^3$ | | |
| 368 | No Abnormalities Detected | 0-20 |
| 369 | No Abnormalities Detected | 0-4, 11-13, 15-20 |
| | Material around eyes, Red, Eye/left | 5-10, 14 |
| | Material around eyes, Red, Eye/right | 5-8 |
| 370 | No Abnormalities Detected | 0-1, 8-13, 15-17, 19-20 |
| | Material around eyes, Red, Eye/left | 2-7, 14, 18 |
| | Material around eyes, Red, Eye/right | 2-6 |
| | Material around nose, Red | 5-6 |
| 371 | No Abnormalities Detected | 0-3, 5-12, 16-17, 20 |
| | Material around eyes, Red, Eye/left | 4, 13-15, 18-19 |
| | Material around eyes, Red, Eye/right | 4, 13, 18-19 |
| 372 | No Abnormalities Detected | 0, 6-7, 15-20 |
| | Material around eyes, Black, Eye/left | 11 |
| | Material around eyes, Black, Eye/right | 11 |
| | Material around eyes, Brown, Eye/left | 3 |
| | Material around eyes, Brown, Eye/right | 3 |
| | Material around eyes, Red, Eye/left | 1-2, 4-5, 8-10, 12-14 |
| | Material around eyes, Red, Eye/right | 1-2, 4-5, 8-10, 12-14 |
| 373 | No Abnormalities Detected | 2-11 |
| | Hair sparse, Forefoot/right | 12-13 |
| | Hair sparse, Forelimb/right | 14-20 |
| | Material around eyes, Red, Eye/left | 0-1, 12 |
| | Material around eyes, Red, Eye/right | 0-1 |
| 374 | No Abnormalities Detected | 0-6 |
| | Hair sparse, Forefoot/left | 7-8 |
| | Hair sparse, Forefoot/right | 7-8 |
| | Hair sparse, Forelimb/left | 9-20 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 4.4 mg/M$^3$ | | |
| | Hair sparse, Forelimb/right | 9-20 |
| | Material around eyes, Brown, Eye/left | 10 |
| | Material around eyes, Brown, Eye/right | 10 |
| | Material around eyes, Red, Eye/left | 11-14, 16-19 |
| | Material around eyes, Red, Eye/right | 9, 11-14, 16, 19 |
| 375 | No Abnormalities Detected | 0-2, 4-20 |
| | Material around nose, Black | 3 |
| 376 | No Abnormalities Detected | 0-1, 8-10, 12-20 |
| | Material around eyes, Red, Eye/left | 2-7, 11 |
| | Material around eyes, Red, Eye/right | 2-7, 11 |
| 377 | No Abnormalities Detected | 0-1, 12-19 |
| | Hair sparse, Forelimb/left | 20 |
| | Hair sparse, Forelimb/right | 20 |
| | Material around eyes, Brown, Eye/left | 9 |
| | Material around eyes, Red, Eye/left | 2-8, 10-11 |
| 378 | No Abnormalities Detected | 12-15, 17, 20 |
| | Material around eyes, Brown, Eye/left | 1, 9 |
| | Material around eyes, Brown, Eye/right | 1, 9 |
| | Material around eyes, Red, Eye/left | 0, 2-8, 10-11, 18-19 |
| | Material around eyes, Red, Eye/right | 0, 2-8, 10-11, 16, 18 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 6.3 mg/M$^3$ | | |
| 379 | No Abnormalities Detected | 0-8, 10-17, 19-20 |
| | Material around eyes, Red, Eye/left | 9, 18 |
| | Material around eyes, Red, Eye/right | 9 |
| 380 | No Abnormalities Detected | 0-5, 13-17, 19-20 |
| | Material around eyes, Brown, Eye/left | 8 |
| | Material around eyes, Red, Eye/left | 6-7, 9-12, 18 |
| 381 | No Abnormalities Detected | 0-7, 9-17, 20 |
| | Material around eyes, Red, Eye/left | 8 |
| | Material around eyes, Red, Eye/right | 8, 18-19 |
| | Material around nose, Black | 8 |
| 382 | No Abnormalities Detected | 0-7, 14-20 |
| | Scabbed area, Cervical region | 8-13 |
| 383 | No Abnormalities Detected | 0-20 |
| 384 | No Abnormalities Detected | 0-20 |
| 385 | No Abnormalities Detected | 0-20 |
| 386 | No Abnormalities Detected | 0 |
| | Hair sparse, Forefoot/left | 1-7 |
| | Hair sparse, Forefoot/right | 1-7 |
| | Hair sparse, Forelimb/left | 8-20 |
| | Hair sparse, Forelimb/right | 8-20 |
| | Hair sparse, Hind limb/left | 17 |
| | Material around nose, Red | 5-7, 15 |
| 387 | No Abnormalities Detected | 0-6, 9, 19-20 |
| | Material around eyes, Brown, Eye/left | 14 |
| | Material around eyes, Brown, Eye/right | 14 |
| | Material around eyes, Red, Eye/left | 7-8, 10-13, 15-18 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 6.3 mg/M$^3$ | | |
| | Material around eyes, Red, Eye/right | 7-8, 11-13, 15-16 |
| 388 | No Abnormalities Detected | 0-4, 14-17, 20 |
| | Material around eyes, Brown, Eye/left | 6 |
| | Material around eyes, Brown, Eye/right | 6 |
| | Material around eyes, Red, Eye/left | 5, 7-13, 18-19 |
| | Material around eyes, Red, Eye/right | 5, 7-13, 18 |
| | Material around nose, Red | 7 |
| 389 | No Abnormalities Detected | 7-8, 12-15, 18-20 |
| | Material around eyes, Red, Eye/left | 0-6, 9, 16-17 |
| | Material around eyes, Red, Eye/right | 0-5, 9-11, 16-17 |
| 390 | No Abnormalities Detected | 0-2 |
| | Hair absent, Forelimb/left | 5-17 |
| | Hair absent, Forelimb/right | 5-17 |
| | Hair sparse, Forefoot/left | 3-4 |
| | Hair sparse, Forefoot/right | 3-4 |
| | Hair sparse, Forelimb/left | 18-20 |
| | Hair sparse, Forelimb/right | 18-20 |
| | Material around eyes, Red, Eye/left | 6-7, 9 |
| | Material around eyes, Red, Eye/right | 9, 16-17 |
| 391 | No Abnormalities Detected | 0-3, 5-20 |
| | Material around eyes, Red, Eye/left | 4 |
| | Material around eyes, Red, Eye/right | 4 |
| 392 | No Abnormalities Detected | 0-2, 5-20 |
| | Material around eyes, Red, Eye/left | 3-4 |
| | Material around eyes, Red, Eye/right | 3-4 |
| 393 | No Abnormalities Detected | 0-14, 16-20 |
| | Material around eyes, Red, Eye/left | 15 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 6.3 mg/M$^3$ | | |
| 394 | No Abnormalities Detected | 0-20 |
| 395 | No Abnormalities Detected | 0-1, 6-7, 9-13 |
| | Hair sparse, Forefoot/left | 2-5, 14-15 |
| | Hair sparse, Forefoot/right | 2-5, 14-15 |
| | Hair sparse, Forelimb/left | 16-20 |
| | Hair sparse, Forelimb/right | 16-20 |
| | Material around eyes, Red, Eye/left | 8 |
| | Material around eyes, Red, Eye/right | 15 |
| | Material around nose, Brown | 4 |
| | Material around nose, Red | 3 |
| 396 | No Abnormalities Detected | 0 |
| | Hair sparse, Forefoot/left | 9-10 |
| | Hair sparse, Forefoot/right | 9-10 |
| | Hair sparse, Forelimb/left | 1-8, 11-20 |
| | Hair sparse, Forelimb/right | 1-8, 11-20 |
| | Material around eyes, Red, Eye/left | 5-6, 14-16 |
| | Material around eyes, Red, Eye/right | 2-6, 19 |
| 397 | No Abnormalities Detected | 0-5 |
| | Hair absent, Hind limb/left | 18-20 |
| | Hair absent, Ventral surface | 11-20 |
| | Hair sparse, Ventral surface | 6-10 |
| | Material around eyes, Red, Eye/right | 13-14 |
| 398 | No Abnormalities Detected | 0-20 |
| 399 | No Abnormalities Detected | 0-12, 14-20 |
| | Material around eyes, Red, Eye/left | 13 |
| 400 | No Abnormalities Detected | 0-2, 5, 9-15, 18-20 |
| | Material around eyes, Red, Eye/left | 4, 6-8, 16-17 |

**Individual Gestation Clinical Findings**

| Group, Animal Number | | Gestation Day Sign Present |
|---|---|---|
| 6.3 mg/M$^3$ | | |
| | Material around eyes, Red, Eye/right | 3-4, 6 |
| 401 | No Abnormalities Detected | 1-2, 4-20 |
| | Material around eyes, Red, Eye/right | 0, 3 |
| 402 | No Abnormalities Detected | 0-1, 5-15, 17-20 |
| | Material around eyes, Red, Eye/right | 2-4 |
| | Material around nose, Red | 2, 16 |
| 403 | No Abnormalities Detected | 0, 4-5, 13-14, 16-20 |
| | Material around eyes, Brown, Eye/left | 9 |
| | Material around eyes, Brown, Eye/right | 9 |
| | Material around eyes, Red, Eye/left | 1-3, 6-8, 10-11, 15 |
| | Material around eyes, Red, Eye/right | 1-3, 6-8, 10, 12, 15 |
| 404 | No Abnormalities Detected | 0-20 |

# APPENDIX E
Individual Gestation Body Weight and Body Weight Change Values

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Gestation Body Weight Values, g**

| Group, Animal Number | Day of Gestation 0 | 3 | 6 | 9 | 12 | 15 | 18 | 20 |
|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | |
| 301 | 239 | 246 | 260 | 268 | 285 | 305 | 336 | 349 |
| 302 | 219 | 236 | 251 | 252 | 270 | 286 | 312 | 337 |
| 303 | 210 | 224 | 236 | 243 | 259 | 276 | 303 | 337 |
| 304 | 229 | 246 | 262 | 265 | 287 | 316 | 340 | 371 |
| 305 | 233 | 248 | 269 | 279 | 300 | 313 | 355 | 377 |
| 306 | 193 | 207 | 216 | 228 | 239 | 245 | 255 | 268 |
| 307 | 221 | 229 | 244 | 252 | 270 | 288 | 321 | 350 |
| 308 | 244 | 258 | 271 | 278 | 288 | 307 | 332 | 359 |
| 309 | 218 | 231 | 242 | 256 | 270 | 283 | 310 | 335 |
| 310 | 231 | 243 | 253 | 275 | 283 | 299 | 340 | 380 |
| 311 | 246 | 259 | 265 | 275 | 289 | 307 | 342 | 370 |
| 312 | 233 | 245 | 250 | 256 | 281 | 302 | 330 | 360 |
| 313 | 236 | 252 | 259 | 262 | 284 | 311 | 339 | 369 |
| 314 x NP | 210 | 230 | 233 | 246 | 246 | 233 | 225 | 235 |
| 315 | 220 | 235 | 244 | 255 | 268 | 290 | 323 | 351 |
| 316 | 236 | 241 | 246 | 256 | 262 | 280 | 308 | 332 |
| 317 | 235 | 249 | 258 | 265 | 278 | 288 | 326 | 355 |
| 318 | 253 | 270 | 279 | 292 | 310 | 324 | 362 | 385 |
| 319 | 238 | 251 | 260 | 277 | 299 | 308 | 348 | 383 |
| 320 | 243 | 260 | 267 | 276 | 292 | 300 | 330 | 351 |
| 321 | 244 | 240 | 242 | 250 | 263 | 275 | 298 | 335 |
| 322 | 234 | 241 | 249 | 269 | 287 | 307 | 333 | 367 |
| 323 | 239 | 245 | 254 | 276 | 297 | 305 | 358 | 393 |
| 324 | 249 | 262 | 263 | 274 | 292 | 302 | 348 | 376 |
| 325 | 260 | 266 | 282 | 294 | 307 | 329 | 365 | 399 |
| 326 | 239 | 255 | 261 | 276 | 280 | 303 | 336 | 370 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Body Weight Values, g**

| Group, Animal Number | Day of Gestation 0 | 3 | 6 | 9 | 12 | 15 | 18 | 20 |
|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | |
| 327 | 199 | 209 | 218 | 228 | 244 | 263 | 295 | 305 |
| 328 | 240 | 260 | 273 | 280 | 300 | 317 | 355 | 382 |
| 329 | 228 | 253 | 267 | 282 | 295 | 321 | 358 | 367 |
| 330 | 234 | 252 | 264 | 279 | 296 | 321 | 357 | 391 |
| 331 | 211 | 220 | 231 | 240 | 255 | 262 | 298 | 319 |
| 332 | 243 | 260 | 271 | 287 | 306 | 323 | 355 | 384 |
| 333 | 214 | 221 | 225 | 234 | 246 | 267 | 291 | 313 |
| 334 | 212 | 226 | 240 | 245 | 270 | 272 | 300 | 342 |
| 335 | 243 | 264 | 276 | 284 | 299 | 321 | 361 | 391 |
| 336 | 216 | 239 | 249 | 263 | 286 | 292 | 335 | 361 |
| 337 | 247 | 263 | 277 | 287 | 289 | 301 | 325 | 347 |
| 338 | 238 | 251 | 255 | 262 | 272 | 281 | 287 | 298 |
| 339 | 217 | 227 | 237 | 248 | 266 | 289 | 311 | 339 |
| 340 x NP | 245 | 251 | 252 | 248 | 254 | 257 | 263 | 258 |
| 341 | 219 | 233 | 237 | 250 | 268 | 278 | 299 | 323 |
| 342 | 251 | 254 | 259 | 268 | 287 | 303 | 334 | 360 |
| 343 | 217 | 228 | 233 | 246 | 266 | 275 | 314 | 344 |
| 344 | 209 | 209 | 215 | 225 | 234 | 252 | 292 | 320 |
| 345 | 229 | 234 | 240 | 247 | 257 | 273 | 311 | 328 |
| 346 | 245 | 252 | 256 | 272 | 290 | 307 | 345 | 377 |
| 347 | 228 | 236 | 248 | 260 | 266 | 279 | 315 | 344 |
| 348 | 230 | 248 | 259 | 265 | 282 | 295 | 343 | 373 |
| 349 | 244 | 257 | 264 | 269 | 285 | 297 | 330 | 353 |
| 350 | 234 | 252 | 268 | 277 | 287 | 306 | 341 | 366 |
| 351 | 248 | 260 | 273 | 285 | 296 | 318 | 361 | 395 |
| 352 | 237 | 244 | 255 | 273 | 289 | 310 | 350 | 390 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Body Weight Values, g**

| Group, Animal Number | Day of Gestation 0 | 3 | 6 | 9 | 12 | 15 | 18 | 20 |
|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | |
| 353 | 212 | 227 | 235 | 242 | 264 | 277 | 309 | 332 |
| 354 | 228 | 246 | 265 | 277 | 288 | 303 | 347 | 370 |
| 355 | 239 | 262 | 275 | 286 | 310 | 329 | 357 | 386 |
| 356 | 208 | 228 | 238 | 254 | 263 | 282 | 324 | 356 |
| 357 | 234 | 248 | 262 | 273 | 297 | 310 | 358 | 397 |
| 358 | 218 | 225 | 236 | 245 | 266 | 277 | 301 | 332 |
| 359 | 234 | 251 | 267 | 278 | 294 | 300 | 326 | 361 |
| 360 | 244 | 258 | 259 | 272 | 285 | 302 | 347 | 376 |
| 361 | 224 | 248 | 262 | 270 | 292 | 304 | 350 | 383 |
| 362 | 252 | 273 | 274 | 295 | 310 | 317 | 347 | 383 |
| 363 | 215 | 236 | 239 | 255 | 273 | 291 | 339 | 373 |
| 364 | 240 | 252 | 252 | 257 | 273 | 294 | 329 | 364 |
| 365 | 219 | 245 | 254 | 270 | 282 | 297 | 338 | 369 |
| 366 | 245 | 258 | 264 | 275 | 293 | 300 | 331 | 361 |
| 367 | 215 | 240 | 243 | 259 | 276 | 283 | 323 | 349 |
| 368 | 255 | 265 | 270 | 288 | 293 | 323 | 355 | 382 |
| 369 | 230 | 246 | 255 | 270 | 278 | 293 | 326 | 355 |
| 370 | 234 | 245 | 252 | 264 | 279 | 297 | 334 | 363 |
| 371 | 244 | 260 | 266 | 284 | 291 | 305 | 335 | 355 |
| 372 | 219 | 228 | 242 | 263 | 276 | 302 | 340 | 367 |
| 373 | 247 | 247 | 250 | 261 | 278 | 295 | 324 | 350 |
| 374 | 238 | 247 | 256 | 276 | 287 | 321 | 370 | 406 |
| 375 | 270 | 279 | 288 | 295 | 312 | 329 | 371 | 397 |
| 376 | 250 | 259 | 268 | 275 | 294 | 309 | 343 | 378 |
| 377 | 249 | 262 | 267 | 283 | 302 | 314 | 355 | 374 |
| 378 | 257 | 257 | 266 | 277 | 293 | 315 | 347 | 383 |

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Gestation Body Weight Values, g**

| Group, Animal Number | Day of Gestation 0 | 3 | 6 | 9 | 12 | 15 | 18 | 20 |
|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | |
| 379 | 204 | 216 | 224 | 232 | 251 | 263 | 298 | 325 |
| 380 | 239 | 252 | 261 | 271 | 281 | 305 | 331 | 358 |
| 381 | 204 | 228 | 231 | 256 | 270 | 293 | 330 | 360 |
| 382 | 227 | 235 | 244 | 252 | 266 | 293 | 317 | 350 |
| 383 | 245 | 264 | 277 | 287 | 313 | 327 | 371 | 398 |
| 384 | 228 | 241 | 253 | 262 | 280 | 293 | 337 | 367 |
| 385 | 259 | 272 | 282 | 296 | 313 | 330 | 357 | 391 |
| 386 | 249 | 281 | 292 | 302 | 323 | 337 | 388 | 423 |
| 387 | 219 | 234 | 239 | 250 | 264 | 279 | 316 | 344 |
| 388 | 239 | 254 | 263 | 271 | 285 | 300 | 342 | 377 |
| 389 | 225 | 235 | 245 | 248 | 274 | 294 | 331 | 355 |
| 390 | 248 | 266 | 272 | 279 | 294 | 322 | 351 | 372 |
| 391 | 226 | 233 | 241 | 252 | 264 | 282 | 311 | 333 |
| 392 | 258 | 271 | 276 | 286 | 304 | 321 | 365 | 385 |
| 393 | 240 | 245 | 257 | 265 | 273 | 298 | 334 | 361 |
| 394 | 227 | 237 | 246 | 256 | 268 | 282 | 312 | 336 |
| 395 | 238 | 239 | 246 | 257 | 266 | 283 | 320 | 354 |
| 396 | 259 | 276 | 283 | 295 | 316 | 339 | 377 | 415 |
| 397 x NP | 264 | 266 | 285 | 298 | 285 | 285 | 285 | 284 |
| 398 | 252 | 252 | 266 | 278 | 289 | 303 | 327 | 348 |
| 399 | 253 | 265 | 278 | 289 | 307 | 318 | 353 | 391 |
| 400 | 236 | 254 | 262 | 271 | 277 | 288 | 318 | 341 |
| 401 | 239 | 250 | 256 | 267 | 288 | 308 | 349 | 384 |
| 402 | 255 | 270 | 275 | 290 | 302 | 323 | 347 | 378 |
| 403 | 252 | 264 | 270 | 280 | 307 | 322 | 359 | 393 |
| 404 | 233 | 237 | 251 | 267 | 277 | 290 | 319 | 348 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Body Weight Change Values, g**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | |
| 301 | 7 | 14 | 8 | 17 | 20 | 31 | 13 | 110 |
| 302 | 17 | 15 | 1 | 18 | 16 | 26 | 25 | 118 |
| 303 | 14 | 12 | 7 | 16 | 17 | 27 | 34 | 127 |
| 304 | 17 | 16 | 3 | 22 | 29 | 24 | 31 | 142 |
| 305 | 15 | 21 | 10 | 21 | 13 | 42 | 22 | 144 |
| 306 | 14 | 9 | 12 | 11 | 6 | 10 | 13 | 75 |
| 307 | 8 | 15 | 8 | 18 | 18 | 33 | 29 | 129 |
| 308 | 14 | 13 | 7 | 10 | 19 | 25 | 27 | 115 |
| 309 | 13 | 11 | 14 | 14 | 13 | 27 | 25 | 117 |
| 310 | 12 | 10 | 22 | 8 | 16 | 41 | 40 | 149 |
| 311 | 13 | 6 | 10 | 14 | 18 | 35 | 28 | 124 |
| 312 | 12 | 5 | 6 | 25 | 21 | 28 | 30 | 127 |
| 313 | 16 | 7 | 3 | 22 | 27 | 28 | 30 | 133 |
| 314 x NP | 20 | 3 | 13 | 0 | -13 | -8 | 10 | 25 |
| 315 | 15 | 9 | 11 | 13 | 22 | 33 | 28 | 131 |
| 316 | 5 | 5 | 10 | 6 | 18 | 28 | 24 | 96 |
| 317 | 14 | 9 | 7 | 13 | 10 | 38 | 29 | 120 |
| 318 | 17 | 9 | 13 | 18 | 14 | 38 | 23 | 132 |
| 319 | 13 | 9 | 17 | 22 | 9 | 40 | 35 | 145 |
| 320 | 17 | 7 | 9 | 16 | 8 | 30 | 21 | 108 |
| 321 | -4 | 2 | 8 | 13 | 12 | 23 | 37 | 91 |
| 322 | 7 | 8 | 20 | 18 | 20 | 26 | 34 | 133 |
| 323 | 6 | 9 | 22 | 21 | 8 | 53 | 35 | 154 |
| 324 | 13 | 1 | 11 | 18 | 10 | 46 | 28 | 127 |
| 325 | 6 | 16 | 12 | 13 | 22 | 36 | 34 | 139 |
| 326 | 16 | 6 | 15 | 4 | 23 | 33 | 34 | 131 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Body Weight Change Values, g**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | |
| 327 | 10 | 9 | 10 | 16 | 19 | 32 | 10 | 106 |
| 328 | 20 | 13 | 7 | 20 | 17 | 38 | 27 | 142 |
| 329 | 25 | 14 | 15 | 13 | 26 | 37 | 9 | 139 |
| 330 | 18 | 12 | 15 | 17 | 25 | 36 | 34 | 157 |
| 331 | 9 | 11 | 9 | 15 | 7 | 36 | 21 | 108 |
| 332 | 17 | 11 | 16 | 19 | 17 | 32 | 29 | 141 |
| 333 | 7 | 4 | 9 | 12 | 21 | 24 | 22 | 99 |
| 334 | 14 | 14 | 5 | 25 | 2 | 28 | 42 | 130 |
| 335 | 21 | 12 | 8 | 15 | 22 | 40 | 30 | 148 |
| 336 | 23 | 10 | 14 | 23 | 6 | 43 | 26 | 145 |
| 337 | 16 | 14 | 10 | 2 | 12 | 24 | 22 | 100 |
| 338 | 13 | 4 | 7 | 10 | 9 | 6 | 11 | 60 |
| 339 | 10 | 10 | 11 | 18 | 23 | 22 | 28 | 122 |
| 340 x NP | 6 | 1 | -4 | 6 | 3 | 6 | -5 | 13 |
| 341 | 14 | 4 | 13 | 18 | 10 | 21 | 24 | 104 |
| 342 | 3 | 5 | 9 | 19 | 16 | 31 | 26 | 109 |
| 343 | 11 | 5 | 13 | 20 | 9 | 39 | 30 | 127 |
| 344 | 0 | 6 | 10 | 9 | 18 | 40 | 28 | 111 |
| 345 | 5 | 6 | 7 | 10 | 16 | 38 | 17 | 99 |
| 346 | 7 | 4 | 16 | 18 | 17 | 38 | 32 | 132 |
| 347 | 8 | 12 | 12 | 6 | 13 | 36 | 29 | 116 |
| 348 | 18 | 11 | 6 | 17 | 13 | 48 | 30 | 143 |
| 349 | 13 | 7 | 5 | 16 | 12 | 33 | 23 | 109 |
| 350 | 18 | 16 | 9 | 10 | 19 | 35 | 25 | 132 |
| 351 | 12 | 13 | 12 | 11 | 22 | 43 | 34 | 147 |
| 352 | 7 | 11 | 18 | 16 | 21 | 40 | 40 | 153 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Body Weight Change Values, g**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | |
| 353 | 15 | 8 | 7 | 22 | 13 | 32 | 23 | 120 |
| 354 | 18 | 19 | 12 | 11 | 15 | 44 | 23 | 142 |
| 355 | 23 | 13 | 11 | 24 | 19 | 28 | 29 | 147 |
| 356 | 20 | 10 | 16 | 9 | 19 | 42 | 32 | 148 |
| 357 | 14 | 14 | 11 | 24 | 13 | 48 | 39 | 163 |
| 358 | 7 | 11 | 9 | 21 | 11 | 24 | 31 | 114 |
| 359 | 17 | 16 | 11 | 16 | 6 | 26 | 35 | 127 |
| 360 | 14 | 1 | 13 | 13 | 17 | 45 | 29 | 132 |
| 361 | 24 | 14 | 8 | 22 | 12 | 46 | 33 | 159 |
| 362 | 21 | 1 | 21 | 15 | 7 | 30 | 36 | 131 |
| 363 | 21 | 3 | 16 | 18 | 18 | 48 | 34 | 158 |
| 364 | 12 | 0 | 5 | 16 | 21 | 35 | 35 | 124 |
| 365 | 26 | 9 | 16 | 12 | 15 | 41 | 31 | 150 |
| 366 | 13 | 6 | 11 | 18 | 7 | 31 | 30 | 116 |
| 367 | 25 | 3 | 16 | 17 | 7 | 40 | 26 | 134 |
| 368 | 10 | 5 | 18 | 5 | 30 | 32 | 27 | 127 |
| 369 | 16 | 9 | 15 | 8 | 15 | 33 | 29 | 125 |
| 370 | 11 | 7 | 12 | 15 | 18 | 37 | 29 | 129 |
| 371 | 16 | 6 | 18 | 7 | 14 | 30 | 20 | 111 |
| 372 | 9 | 14 | 21 | 13 | 26 | 38 | 27 | 148 |
| 373 | 0 | 3 | 11 | 17 | 17 | 29 | 26 | 103 |
| 374 | 9 | 9 | 20 | 11 | 34 | 49 | 36 | 168 |
| 375 | 9 | 9 | 7 | 17 | 17 | 42 | 26 | 127 |
| 376 | 9 | 9 | 7 | 19 | 15 | 34 | 35 | 128 |
| 377 | 13 | 5 | 16 | 19 | 12 | 41 | 19 | 125 |
| 378 | 0 | 9 | 11 | 16 | 22 | 32 | 36 | 126 |

**Individual Gestation Body Weight Change Values, g**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | |
| 379 | 12 | 8 | 8 | 19 | 12 | 35 | 27 | 121 |
| 380 | 13 | 9 | 10 | 10 | 24 | 26 | 27 | 119 |
| 381 | 24 | 3 | 25 | 14 | 23 | 37 | 30 | 156 |
| 382 | 8 | 9 | 8 | 14 | 27 | 24 | 33 | 123 |
| 383 | 19 | 13 | 10 | 26 | 14 | 44 | 27 | 153 |
| 384 | 13 | 12 | 9 | 18 | 13 | 44 | 30 | 139 |
| 385 | 13 | 10 | 14 | 17 | 17 | 27 | 34 | 132 |
| 386 | 32 | 11 | 10 | 21 | 14 | 51 | 35 | 174 |
| 387 | 15 | 5 | 11 | 14 | 15 | 37 | 28 | 125 |
| 388 | 15 | 9 | 8 | 14 | 15 | 42 | 35 | 138 |
| 389 | 10 | 10 | 3 | 26 | 20 | 37 | 24 | 130 |
| 390 | 18 | 6 | 7 | 15 | 28 | 29 | 21 | 124 |
| 391 | 7 | 8 | 11 | 12 | 18 | 29 | 22 | 107 |
| 392 | 13 | 5 | 10 | 18 | 17 | 44 | 20 | 127 |
| 393 | 5 | 12 | 8 | 8 | 25 | 36 | 27 | 121 |
| 394 | 10 | 9 | 10 | 12 | 14 | 30 | 24 | 109 |
| 395 | 1 | 7 | 11 | 9 | 17 | 37 | 34 | 116 |
| 396 | 17 | 7 | 12 | 21 | 23 | 38 | 38 | 156 |
| 397 x NP | 2 | 19 | 13 | -13 | 0 | 0 | -1 | 20 |
| 398 | 0 | 14 | 12 | 11 | 14 | 24 | 21 | 96 |
| 399 | 12 | 13 | 11 | 18 | 11 | 35 | 38 | 138 |
| 400 | 18 | 8 | 9 | 6 | 11 | 30 | 23 | 105 |
| 401 | 11 | 6 | 11 | 21 | 20 | 41 | 35 | 145 |
| 402 | 15 | 5 | 15 | 12 | 21 | 24 | 31 | 123 |
| 403 | 12 | 6 | 10 | 27 | 15 | 37 | 34 | 141 |
| 404 | 4 | 14 | 16 | 10 | 13 | 29 | 29 | 115 |

NP - Not Pregnant

x - Excluded from summary statistics

# APPENDIX F
Individual Gestation Food Consumption Values

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Gestation Food Consumption Values, g/animal/day**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | |
| 301 | 18.0 | 21.3 | 20.3 | 21.3 | 24.3 | 24.3 | 14.5 | 20.9 |
| 302 | 20.0 | 22.3 | 19.3 | 21.0 | 22.7 | 22.0 | 18.5 | 21.0 |
| 303 | 17.3 | 19.0 | 18.7 | 20.0 | 22.7 | 21.7 | 24.5 | 20.4 |
| 304 | 21.7 | 23.0 | 21.0 | 23.7 | 27.0 | 24.3 | 23.5 | 23.5 |
| 305 | 22.7 | 25.3 | 24.3 | 27.0 | 25.0 | 29.7 | 25.0 | 25.6 |
| 306 | 18.3 | 19.7 | 19.3 | 21.0 | 22.0 | 19.0 | 20.0 | 19.9 |
| 307 | 19.0 | 20.7 | 20.3 | 22.3 | 22.7 | 23.0 | 18.5 | 21.1 |
| 308 | 20.7 | 21.0 | 20.7 | 21.0 | 23.0 | 20.7 | 22.0 | 21.3 |
| 309 | 19.0 | 20.3 | 20.7 | 22.3 | 23.0 | 20.0 | 22.0 | 21.0 |
| 310 | 21.0 | 22.3 | 24.0 | 23.3 | 25.7 | 24.7 | 29.5 | 24.1 |
| 311 | 21.3 | 21.7 | 21.3 | 22.3 | 19.7 | 29.0 | 27.0 | 23.0 |
| 312 | 18.7 | 19.0 | 18.7 | 21.3 | 24.0 | 21.3 | 22.5 | 20.7 |
| 313 | 20.7 | 20.7 | 19.3 | 22.7 | 27.3 | 20.7 | 26.5 | 22.4 |
| 314 x NP | 19.7 | 18.0 | 20.3 | 18.7 | 13.3 | 13.7 | 16.0 | 17.2 |
| 315 | 19.0 | 19.3 | 19.3 | 22.3 | 22.7 | 21.7 | 21.0 | 20.8 |
| 316 | 18.0 | 18.0 | 19.0 | 20.0 | 20.7 | 18.3 | 21.5 | 19.3 |
| 317 | 20.3 | 20.0 | 19.7 | 19.7 | 18.7 | 21.0 | 21.0 | 20.0 |
| 318 | 20.3 | 20.3 | 22.3 | 24.0 | 22.3 | 26.0 | 27.0 | 23.0 |
| 319 | 20.0 | 20.0 | 22.7 | 24.3 | 22.7 | 23.0 | 29.5 | 22.9 |
| 320 | 22.0 | 21.3 | 23.3 | 23.3 | 23.7 | 23.0 | 21.0 | 22.6 |
| 321 | 15.7 | 16.3 | 18.0 | 18.0 | 17.3 | 17.3 | 25.5 | 18.0 |
| 322 | 17.3 | 19.0 | 21.3 | 23.3 | 22.7 | 20.7 | 28.5 | 21.5 |
| 323 | 17.3 | 19.3 | 21.3 | 23.0 | 20.3 | 27.7 | 26.5 | 22.0 |
| 324 | 18.7 | 18.0 | 20.0 | 19.0 | 18.3 | 26.3 | 24.5 | 20.5 |
| 325 | 20.0 | 23.0 | 22.7 | 21.7 | 24.7 | 27.7 | 29.5 | 23.9 |
| 326 | 19.7 | 18.7 | 22.3 | 19.7 | 16.7 | 25.7 | 28.5 | 21.3 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Food Consumption Values, g/animal/day**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | |
| 327 | 12.3 | 23.3 | 18.3 | 19.3 | 22.7 | 23.7 | 17.5 | 19.7 |
| 328 | 20.7 | 24.0 | 22.0 | 22.7 | 25.3 | 24.3 | 26.0 | 23.5 |
| 329 | 22.3 | 24.3 | 22.7 | 24.3 | 27.0 | 29.0 | 19.5 | 24.4 |
| 330 | 21.0 | 20.7 | 23.7 | 23.3 | 26.0 | 24.3 | 26.5 | 23.5 |
| 331 | 18.3 | 20.7 | 19.3 | 20.7 | 21.3 | 20.0 | 20.0 | 20.1 |
| 332 | 21.0 | 22.0 | 22.7 | 23.7 | 24.0 | 25.3 | 25.5 | 23.4 |
| 333 | 17.0 | 17.7 | 17.3 | 18.3 | 21.3 | 20.3 | 19.5 | 18.8 |
| 334 | 19.7 | 21.0 | 21.3 | 22.0 | 17.3 | 20.0 | 25.5 | 20.8 |
| 335 | 21.7 | 23.3 | 22.7 | 23.7 | 22.0 | 28.7 | 28.0 | 24.1 |
| 336 | 21.0 | 20.3 | 32.0 | 24.0 | 21.3 | 27.7 | 29.0 | 24.9 |
| 337 | 20.0 | 20.3 | 21.7 | 20.0 | 22.3 | 20.3 | 25.0 | 21.2 |
| 338 | 19.7 | 20.0 | 19.3 | 20.7 | 22.3 | 18.7 | 21.5 | 20.3 |
| 339 | 18.0 | 19.3 | 20.0 | 22.0 | 26.3 | 19.7 | 22.0 | 21.0 |
| 340 x NP | 17.7 | 18.7 | 17.0 | 18.0 | 15.7 | 17.3 | 15.0 | 17.2 |
| 341 | 19.7 | 18.7 | 20.0 | 21.7 | 22.0 | 21.3 | 25.5 | 21.1 |
| 342 | 18.3 | 19.7 | 20.3 | 24.0 | 20.3 | 25.3 | 23.5 | 21.6 |
| 343 | 19.3 | 19.7 | 20.7 | 23.3 | 21.0 | 24.0 | 26.0 | 21.8 |
| 344 | 16.0 | 17.7 | 17.3 | 17.3 | 18.7 | 21.7 | 21.0 | 18.4 |
| 345 | 17.7 | 17.7 | 18.7 | 18.7 | 21.7 | 23.7 | 24.0 | 20.1 |
| 346 | 19.0 | 20.0 | 20.3 | 23.3 | 30.7 | 26.0 | 27.5 | 23.7 |
| 347 | 17.3 | 19.7 | 20.7 | 18.3 | 21.3 | 24.0 | 25.0 | 20.7 |
| 348 | 19.0 | 20.3 | 20.3 | 20.3 | 21.3 | 28.0 | 26.5 | 22.1 |
| 349 | 20.0 | 21.3 | 22.7 | 22.7 | 24.7 | 25.3 | 30.0 | 23.5 |
| 350 | 20.7 | 24.3 | 23.3 | 30.0 | 24.7 | 29.7 | 26.5 | 25.6 |
| 351 | 19.0 | 20.7 | 22.3 | 22.0 | 23.0 | 28.0 | 34.0 | 23.7 |
| 352 | 18.3 | 21.0 | 22.0 | 22.0 | 24.7 | 28.7 | 26.5 | 23.2 |

NP - Not Pregnant

x - Excluded from summary statistics

**Individual Gestation Food Consumption Values, g/animal/day**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | |
| 353 | 20.3 | 20.7 | 19.0 | 20.7 | 21.0 | 22.3 | 22.5 | 20.9 |
| 354 | 20.7 | 21.7 | 19.3 | 22.7 | 22.7 | 29.0 | 23.5 | 22.8 |
| 355 | 21.0 | 22.7 | 22.7 | 24.7 | 25.0 | 28.3 | 30.5 | 24.7 |
| 356 | 19.3 | 19.7 | 21.7 | 21.0 | 21.3 | 25.3 | 27.0 | 22.0 |
| 357 | 22.7 | 23.3 | 23.3 | 25.0 | 22.3 | 28.3 | 29.0 | 24.7 |
| 358 | 18.7 | 20.0 | 19.3 | 22.3 | 20.3 | 21.7 | 23.5 | 20.7 |
| 359 | 23.0 | 25.0 | 23.3 | 24.0 | 20.7 | 22.0 | 30.0 | 23.7 |
| 360 | 21.0 | 20.0 | 22.0 | 19.7 | 24.3 | 28.3 | 26.5 | 23.0 |
| 361 | 22.3 | 24.0 | 23.3 | 27.3 | 23.7 | 29.0 | 30.0 | 25.5 |
| 362 | 22.0 | 21.3 | 23.7 | 24.0 | 21.7 | 23.7 | 29.5 | 23.4 |
| 363 | 18.3 | 18.3 | 20.7 | 22.0 | 22.3 | 27.3 | 28.0 | 22.2 |
| 364 | 20.7 | 18.3 | 19.3 | 20.0 | 23.3 | 24.0 | 25.0 | 21.4 |
| 365 | 21.7 | 22.0 | 22.7 | 23.3 | 22.7 | 30.0 | 27.5 | 24.1 |
| 366 | 21.0 | 20.7 | 21.0 | 23.3 | 20.7 | 25.0 | 28.0 | 22.6 |
| 367 | 21.3 | 20.7 | 22.3 | 24.0 | 21.0 | 26.3 | 25.0 | 22.9 |
| 368 | 20.3 | 18.7 | 29.0 | 10.7 | 29.0 | 28.7 | 27.0 | 23.2 |
| 369 | 20.3 | 21.0 | 22.3 | 20.0 | 23.7 | 26.7 | 23.5 | 22.5 |
| 370 | 18.7 | 20.0 | 21.7 | 21.0 | 26.0 | 25.0 | 23.0 | 22.2 |
| 371 | 22.0 | 22.0 | 23.7 | 22.0 | 25.0 | 28.3 | 29.0 | 24.4 |
| 372 | 19.0 | 20.0 | 25.7 | 45.0 | 27.7 | 30.0 | 28.0 | 27.9 |
| 373 | 16.7 | 16.3 | 20.3 | 21.7 | 21.3 | 25.0 | 25.0 | 20.7 |
| 374 | 19.7 | 19.7 | 22.7 | 22.0 | 25.7 | 32.0 | 30.5 | 24.3 |
| 375 | 20.0 | 20.7 | 22.0 | 23.3 | 24.7 | 27.7 | 26.5 | 23.4 |
| 376 | 17.7 | 21.7 | -15.3[e] | 20.0 | 25.7 | 28.0 | 30.0 | 17.7[e] |
| 377 | 21.7 | 21.3 | 20.3 | 24.3 | 25.3 | 28.0 | 25.5 | 23.7 |
| 378 | 16.7 | 19.3 | 20.3 | 19.7 | 23.7 | 25.7 | 27.0 | 21.5 |

e - Excluded from the mean

**Individual Gestation Food Consumption Values, g/animal/day**

| Group, Animal Number | Day of Gestation 0-3 | 3-6 | 6-9 | 9-12 | 12-15 | 15-18 | 18-20 | 0-20 |
|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | |
| 379 | 19.0 | 19.7 | 19.0 | 20.7 | 19.3 | 23.7 | 23.0 | 20.5 |
| 380 | 20.3 | 22.3 | 21.0 | 20.7 | 24.0 | 22.3 | 25.0 | 22.1 |
| 381 | 21.3 | 23.3 | 22.7 | 22.7 | 25.3 | 26.0 | 25.0 | 23.7 |
| 382 | 19.7 | 19.3 | 20.0 | 20.3 | 22.7 | 21.7 | 24.5 | 21.0 |
| 383 | 24.0 | 25.3 | 24.0 | 27.3 | 26.3 | 32.0 | 28.5 | 26.7 |
| 384 | 21.3 | 22.0 | 20.0 | 23.0 | 22.0 | 27.0 | 29.0 | 23.2 |
| 385 | 23.0 | 24.3 | 23.3 | 26.0 | 27.0 | 27.0 | 29.0 | 25.5 |
| 386 | 23.3 | 23.3 | 23.3 | 24.0 | 23.3 | 26.3 | 28.5 | 24.4 |
| 387 | 20.0 | 19.3 | 20.3 | 21.7 | 21.7 | 26.3 | 25.5 | 22.0 |
| 388 | 20.7 | 20.7 | 19.7 | 22.3 | 21.7 | 27.3 | 29.0 | 22.8 |
| 389 | 16.7 | 20.7 | 19.0 | 21.0 | 24.0 | 26.3 | 25.5 | 21.7 |
| 390 | 23.3 | 23.0 | 23.7 | 23.7 | 28.3 | 29.0 | 24.5 | 25.1 |
| 391 | 18.3 | 19.0 | 19.7 | 21.0 | 21.3 | 24.3 | 24.5 | 21.0 |
| 392 | 21.3 | 21.0 | 23.3 | 26.3 | 27.0 | 30.3 | 27.0 | 25.1 |
| 393 | 19.3 | 21.3 | 21.7 | 22.7 | 23.0 | 29.7 | 25.0 | 23.2 |
| 394 | 21.0 | 19.3 | 20.7 | 21.0 | 22.3 | 25.3 | 25.5 | 22.0 |
| 395 | 18.0 | 21.0 | 21.0 | 20.7 | 22.0 | 25.3 | 26.5 | 21.9 |
| 396 | 21.3 | 20.3 | 22.3 | 22.7 | 26.7 | 27.0 | 26.5 | 23.7 |
| 397 x NP | 20.0 | 22.0 | 22.7 | 19.0 | 23.3 | 16.7 | 19.5 | 20.5 |
| 398 | 16.7 | 19.3 | 20.7 | 20.3 | 23.3 | 26.0 | 25.0 | 21.5 |
| 399 | 21.7 | 22.7 | 23.3 | 25.3 | 26.0 | 28.7 | 31.5 | 25.3 |
| 400 | 21.3 | 21.3 | 22.0 | 21.7 | 22.3 | 25.0 | 26.5 | 22.7 |
| 401 | 19.3 | 21.3 | 21.0 | 25.7 | 25.3 | 27.7 | 27.5 | 23.8 |
| 402 | 21.7 | 21.0 | 21.0 | 23.7 | 27.7 | 26.7 | 28.5 | 24.1 |
| 403 | 20.7 | 21.0 | 20.0 | 25.0 | 24.7 | 28.0 | 31.0 | 24.0 |
| 404 | 20.3 | 22.3 | 21.7 | 22.0 | 23.3 | 25.7 | 27.0 | 23.0 |

NP - Not Pregnant

x - Excluded from summary statistics

# APPENDIX G
RBC Analytical Results

APPENDIX H
Individual Animal Data Record: Pathology

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group, Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 0 mg/M$^3$ (Control) | | | | |
| 301 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 302 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 303 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 304 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 305 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 306 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 307 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 308 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group, Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 0 mg/M$^3$ (Control) | | | | |
| 309 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 310 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 311 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 312 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 313 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 314 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 315 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 316 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 317 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 318 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 0 mg/M$^3$ (Control) | | | | |
| 319 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 320 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 321 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 322 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 323 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 324 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |
| 325 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 326 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | |
| 327 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 328 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 329 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 330 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 331 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, mild.<br>- Inflammation, acute, mild.<br>- Macrophages, pigmented alveolar, moderate. |
| 332 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 333 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, mild.<br>- Inflammation, acute, mild.<br>- Macrophages, pigmented alveolar, moderate. |
| 334 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | |
| 335 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 336 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 337 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 338 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 339 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 340 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 341 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 342 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | |
| 343 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 344 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, moderate.<br>- Inflammation, acute, mild.<br>- Macrophages, pigmented alveolar, moderate. |
| 345 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 346 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 347 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | |
| 348 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, minimal. |
| 349 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 350 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, minimal. |
| 351 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 352 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | |
| 353 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 354 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 355 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, minimal. |
| 356 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 357 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 358 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | |
| 359 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 360 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 361 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 362 | F | S | **MACROSCOPIC:** | |
| | | | Lymph Node, Inguinal | - Not identified.<br>- Draining node for mass A. |
| | | | Skin, Subcutis | - Mass, tan, right inguinal, mass A.<br>3.0 x 3.5 x 1.5 cm. Corresponds to antemortem observation. |
| 363 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 364 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 365 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | |
| 366 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 367 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 368 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 369 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 370 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, mild. |
| 371 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | |
| 372 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 373 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 374 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 375 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 376 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 377 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 378 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | |
| 379 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 380 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, moderate. |
| 381 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 382 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 383 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 384 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 385 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, moderate. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | |
| 386 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, moderate. |
| 387 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 388 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 389 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, minimal.<br>- Inflammation, acute, minimal.<br>- Macrophages, pigmented alveolar, moderate. |
| 390 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | |
| 391 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, mild.<br>- Inflammation, acute, mild.<br>- Macrophages, pigmented alveolar, moderate. |
| 392 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 393 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, mild. |
| 394 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 395 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 396 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 397 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 398 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 399 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |



[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

Individual Animal Data Record: Pathology
Terminal Sacrifice: Rat

| Group. Animal Number | Sex | Fate[1] | Tissue: | Observations: |
|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | |
| 400 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 401 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Hyperplasia, type II cell, mild.<br>- Inflammation, acute, mild.<br>- Macrophages, pigmented alveolar, moderate. |
| 402 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| | | | **MICROSCOPIC:** | |
| | | | Lung | - Macrophages, pigmented alveolar, moderate. |
| 403 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |
| 404 | F | S | **MACROSCOPIC:** | |
| | | | All Tissues | - Within normal limits. |





[1]FATE CODES: S=SCHEDULED SACRIFICE E=SACRIFICED IN EXTREMIS D=DIED ON STUDY

# APPENDIX I
Individual Organ Weight Values

Codes For Individual Organ Weight Values

Terminal Sacrifice

*Data not available

Individual Organ Weight Values - Terminal Sacrifice

| Group, Animal Number | Sex | Brain g | Lung g | Lung/Brain Weight %x10$^{-1}$ |
|---|---|---|---|---|
| 0 mg/M3 (Control): | | | | |
| 301 | F | 1.78 | 1.22 | 6.85 |
| 302 | F | 1.57 | 1.24 | 7.88 |
| 303 | F | 1.71 | 1.41 | 8.23 |
| 304 | F | 1.71 | 1.73 | 10.13 |
| 305 | F | 1.66 | 1.34 | 8.04 |
| 306 | F | 1.50 | 1.08 | 7.19 |
| 307 | F | 1.83 | 1.61 | 8.81 |
| 308 | F | 1.81 | 1.66 | 9.19 |
| 309 | F | 1.46 | 1.23 | 8.45 |
| 310 | F | 1.83 | 1.24 | 6.78 |
| 311 | F | 1.66 | 1.38 | 8.30 |
| 312 | F | 1.83 | 1.36 | 7.40 |
| 313 | F | 1.72 | 1.18 | 6.86 |
| 314 | F | 1.70 | 1.18 | 6.94 |
| 315 | F | 1.75 | 1.23 | 7.04 |
| 316 | F | 1.72 | 1.42 | 8.24 |
| 317 | F | 1.82 | 1.32 | 7.26 |
| 318 | F | 1.58 | 1.48 | 9.38 |
| 319 | F | 1.59 | 1.36 | 8.61 |
| 320 | F | 1.67 | 1.12 | 6.70 |
| 321 | F | * | 1.22 | * |
| 322 | F | 1.61 | 1.28 | 7.98 |
| 323 | F | 1.72 | 1.22 | 7.07 |
| 324 | F | 1.60 | 1.24 | 7.77 |
| 325 | F | 1.75 | 1.33 | 7.61 |
| 326 | F | 1.66 | 1.37 | 8.26 |

Individual Organ Weight Values - Terminal Sacrifice

| Group, Animal Number | Sex | Brain g | Lung g | Lung/Brain Weight %x10 $^{-1}$ |
|---|---|---|---|---|
| 2.6 mg/M3: | | | | |
| 327 | F | 1.84 | 1.24 | 6.75 |
| 328 | F | 1.98 | 1.74 | 8.79 |
| 329 | F | 1.75 | 1.65 | 9.45 |
| 330 | F | 1.73 | 1.57 | 9.03 |
| 331 | F | 1.60 | 1.76 | 10.98 |
| 332 | F | 1.76 | 1.67 | 9.47 |
| 333 | F | 1.68 | 1.54 | 9.17 |
| 334 | F | 1.70 | 1.66 | 9.75 |
| 335 | F | 1.71 | 1.68 | 9.86 |
| 336 | F | 1.70 | 2.15 | 12.67 |
| 337 | F | 1.61 | 1.56 | 9.68 |
| 338 | F | 1.82 | 1.50 | 8.24 |
| 339 | F | 1.79 | 1.37 | 7.66 |
| 340 | F | 1.94 | 1.67 | 8.62 |
| 341 | F | 1.64 | 1.41 | 8.60 |
| 342 | F | 1.57 | 1.62 | 10.32 |
| 343 | F | 1.62 | 1.56 | 9.65 |
| 344 | F | 1.75 | 1.90 | 10.82 |
| 345 | F | 1.71 | 1.57 | 9.20 |
| 346 | F | 1.83 | 1.66 | 9.11 |
| 347 | F | 1.71 | 1.83 | 10.70 |
| 348 | F | 1.83 | 1.82 | 9.95 |
| 349 | F | 1.81 | 1.44 | 7.99 |
| 350 | F | 1.70 | 1.70 | 10.04 |
| 351 | F | 1.86 | 1.69 | 9.06 |
| 352 | F | 1.68 | 1.79 | 10.67 |

Individual Organ Weight Values - Terminal Sacrifice

| Group, Animal Number | Sex | Brain g | Lung g | Lung/Brain Weight %x10 |
|---|---|---|---|---|
| 4.4 mg/M3: | | | | |
| 353 | F | 1.55 | 1.35 | 8.72 |
| 354 | F | 1.83 | 1.65 | 9.03 |
| 355 | F | 1.75 | 1.74 | 9.98 |
| 356 | F | 1.87 | 1.51 | 8.05 |
| 357 | F | 1.81 | 2.01 | 11.10 |
| 358 | F | 1.93 | 1.68 | 8.70 |
| 359 | F | 1.71 | 1.79 | 10.48 |
| 360 | F | 1.71 | 1.46 | 8.52 |
| 361 | F | 1.57 | 1.73 | 10.96 |
| 362 | F | 1.83 | 1.88 | 10.23 |
| 363 | F | 1.70 | 1.54 | 9.04 |
| 364 | F | 1.66 | 1.62 | 9.71 |
| 365 | F | 1.74 | 1.74 | 10.01 |
| 366 | F | 1.65 | 1.78 | 10.74 |
| 367 | F | 1.78 | 1.78 | 9.96 |
| 368 | F | 1.83 | 1.62 | 8.84 |
| 369 | F | 1.76 | 1.75 | 9.92 |
| 370 | F | 1.64 | 1.74 | 10.57 |
| 371 | F | 1.70 | 1.82 | 10.73 |
| 372 | F | 2.00 | 1.72 | 8.62 |
| 373 | F | 1.63 | 1.47 | 8.98 |
| 374 | F | 1.80 | 1.67 | 9.28 |
| 375 | F | 1.64 | 2.13 | 12.98 |
| 376 | F | 1.58 | 1.94 | 12.33 |
| 377 | F | 1.74 | 1.84 | 10.57 |
| 378 | F | 1.83 | 1.95 | 10.61 |

Individual Organ Weight Values - Terminal Sacrifice

| Group, Animal Number | Sex | Brain g | Lung g | Lung/Brain Weight %x10$^{-1}$ |
|---|---|---|---|---|
| 6.3 mg/M3: | | | | |
| 379 | F | 1.80 | 1.51 | 8.43 |
| 380 | F | 1.79 | 1.97 | 11.02 |
| 381 | F | 1.65 | 1.65 | 9.98 |
| 382 | F | 1.85 | 1.94 | 10.49 |
| 383 | F | 1.80 | 1.98 | 10.98 |
| 384 | F | 1.68 | 2.06 | 12.26 |
| 385 | F | 1.96 | 2.28 | 11.65 |
| 386 | F | 1.90 | 1.94 | 10.23 |
| 387 | F | 1.76 | 1.80 | 10.26 |
| 388 | F | 1.99 | 1.83 | 9.18 |
| 389 | F | 1.73 | 1.56 | 9.03 |
| 390 | F | 1.71 | 1.87 | 10.94 |
| 391 | F | 1.78 | 1.62 | 9.08 |
| 392 | F | 1.71 | 1.62 | 9.50 |
| 393 | F | 1.51 | 1.58 | 10.50 |
| 394 | F | 1.67 | 1.84 | 11.00 |
| 395 | F | 1.75 | 1.78 | 10.16 |
| 396 | F | 1.78 | 1.96 | 11.03 |
| 397 | F | 1.71 | 1.91 | 11.16 |
| 398 | F | 1.68 | 1.92 | 11.41 |
| 399 | F | 1.82 | 1.99 | 10.96 |
| 400 | F | 1.63 | 1.77 | 10.88 |
| 401 | F | 1.47 | 1.79 | 12.15 |
| 402 | F | 1.65 | 1.80 | 10.94 |
| 403 | F | 1.65 | 1.67 | 10.07 |
| 404 | F | 1.43 | 1.84 | 12.85 |

# APPENDIX J
Individual Maternal Uterine Implantation Data and Average Fetal Body Weight Values

**Individual Maternal Uterine Implantation Data and Average Fetal Body Weight Values**

| Group, Animal Number | Corpora Lutea | % Preimplantation Loss | Implant Sites | Fetuses Viable | Fetuses Non-Viable[1] | Resorptions Early | Resorptions Late | Resorptions Total | % Postimplantation Loss | Sex Male | Sex Female | Average Fetal Body Weight, g Male | Average Fetal Body Weight, g Female | Average Fetal Body Weight, g Litter |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | | | | | | | |
| 301 | 15 | 6.7 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 3.69 | 3.72 | 3.70 |
| 302 | 16 | 6.3 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 12 | 3 | 3.45 | 3.23 | 3.41 |
| 303 | 13 | 0.0 | 13 | 12 | 0 | 1 | 0 | 1 | 7.7 | 7 | 5 | 3.73 | 3.58 | 3.67 |
| 304 | 15 | 6.7 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 7 | 7 | 3.89 | 3.67 | 3.78 |
| 305 | 20 | 25.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 10 | 5 | 4.04 | 3.86 | 3.98 |
| 306 | 10 | 80.0 | 2 | 2 | 0 | 0 | 0 | 0 | 0.0 | 0 | 2 | NA | 6.70 | 6.70 |
| 307 | 13 | 0.0 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 6 | 7 | 3.75 | 3.43 | 3.58 |
| 308 | 16 | 0.0 | 16 | 15 | 0 | 1 | 0 | 1 | 6.3 | 5 | 10 | 4.02 | 3.84 | 3.90 |
| 309 | 13 | 15.4 | 11 | 11 | 0 | 0 | 0 | 0 | 0.0 | 3 | 8 | 3.47 | 3.29 | 3.34 |
| 310 | 20 | 15.0 | 17 | 15 | 0 | 2 | 0 | 2 | 11.8 | 5 | 10 | 3.90 | 3.84 | 3.86 |
| 311 | 17 | 0.0 | 17 | 15 | 0 | 2 | 0 | 2 | 11.8 | 8 | 7 | 3.59 | 3.37 | 3.49 |
| 312 | 17 | 0.0 | 17 | 17 | 0 | 0 | 0 | 0 | 0.0 | 10 | 7 | 3.40 | 3.14 | 3.29 |
| 313 | 18 | 22.2 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 4 | 10 | 3.57 | 3.44 | 3.48 |
| 314 x NP | | | | | | | | | | | | | | |
| 315 | 21 | 33.3 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 8 | 6 | 3.78 | 3.83 | 3.80 |
| 316 | 17 | 23.5 | 13 | 12 | 0 | 0 | 1 | 1 | 7.7 | 5 | 7 | 3.02 | 2.87 | 2.93 |
| 317 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 11 | 5 | 3.65 | 3.30 | 3.54 |
| 318 | 14 | 0.0 | 14 | 11 | 0 | 3 | 0 | 3 | 21.4 | 8 | 3 | 3.74 | 3.57 | 3.69 |
| 319 | 18 | 0.0 | 18 | 17 | 0 | 1 | 0 | 1 | 5.6 | 10 | 7 | 4.03 | 3.73 | 3.91 |
| 320 | 15 | 13.3 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 6 | 7 | 3.85 | 3.44 | 3.63 |
| 321 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 3.34 | 3.30 | 3.33 |
| 322 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 6 | 8 | 4.12 | 3.69 | 3.87 |
| 323 | 20 | 10.0 | 18 | 17 | 0 | 0 | 1 | 1 | 5.6 | 9 | 8 | 4.00 | 3.56 | 3.79 |
| 324 | 16 | 0.0 | 16 | 15 | 0 | 1 | 0 | 1 | 6.3 | 8 | 7 | 3.65 | 3.50 | 3.58 |
| 325 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 8 | 8 | 3.65 | 3.51 | 3.58 |
| 326 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 2 | 13 | 3.95 | 3.65 | 3.69 |

NP - Not Pregnant
NA - Not Applicable/Not Available
x - Excluded from summary statistics
[1] Nonviable fetus(es) excluded from summary statistics

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Maternal Uterine Implantation Data and Average Fetal Body Weight Values**

| Group, Animal Number | Corpora Lutea | % Preimplantation Loss | Implant Sites | Fetuses Viable | Fetuses Non-Viable[1] | Resorptions Early | Resorptions Late | Resorptions Total | % Postimplantation Loss | Sex Male | Sex Female | Average Fetal Body Weight, g Male | Average Fetal Body Weight, g Female | Average Fetal Body Weight, g Litter |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | | | | | | | |
| 327 | 14 | 14.3 | 12 | 12 | 0 | 0 | 0 | 0 | 0.0 | 9 | 3 | 3.66 | 3.47 | 3.61 |
| 328 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 10 | 6 | 3.79 | 3.50 | 3.68 |
| 329 | 15 | 0.0 | 15 | 14 | 0 | 1 | 0 | 1 | 6.7 | 10 | 4 | 3.88 | 3.75 | 3.84 |
| 330 | 17 | 0.0 | 17 | 15 | 0 | 2 | 0 | 2 | 11.8 | 7 | 8 | 3.70 | 3.69 | 3.69 |
| 331 | 13 | 0.0 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 3 | 10 | 3.60 | 3.43 | 3.47 |
| 332 | 17 | 5.9 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 10 | 6 | 3.56 | 3.37 | 3.49 |
| 333 | 18 | 27.8 | 13 | 11 | 0 | 2 | 0 | 2 | 15.4 | 7 | 4 | 3.60 | 3.43 | 3.54 |
| 334 | 16 | 0.0 | 16 | 15 | 0 | 1 | 0 | 1 | 6.3 | 8 | 7 | 3.64 | 3.31 | 3.49 |
| 335 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 8 | 8 | 3.44 | 3.56 | 3.50 |
| 336 | 13 | 0.0 | 13 | 11 | 0 | 2 | 0 | 2 | 15.4 | 6 | 5 | 4.37 | 4.26 | 4.32 |
| 337 | 14 | 28.6 | 10 | 10 | 0 | 0 | 0 | 0 | 0.0 | 7 | 3 | 3.36 | 3.40 | 3.37 |
| 338 | 6 | 66.7 | 2 | 2 | 0 | 0 | 0 | 0 | 0.0 | 1 | 1 | 4.80 | 3.90 | 4.35 |
| 339 | 15 | 6.7 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 4 | 10 | 3.97 | 3.85 | 3.89 |
| 340 x NP | | | | | | | | | | | | | | |
| 341 | 13 | 7.7 | 12 | 11 | 0 | 1 | 0 | 1 | 8.3 | 3 | 8 | 3.73 | 3.41 | 3.50 |
| 342 | 14 | 7.1 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 7 | 6 | 3.66 | 3.60 | 3.63 |
| 343 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 7 | 8 | 3.84 | 3.26 | 3.53 |
| 344 | 17 | 17.6 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 8 | 6 | 3.74 | 3.65 | 3.70 |
| 345 | 15 | 40.0 | 9 | 9 | 0 | 0 | 0 | 0 | 0.0 | 3 | 6 | 4.00 | 3.63 | 3.76 |
| 346 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 4.02 | 3.96 | 4.00 |
| 347 | 15 | 6.7 | 14 | 13 | 0 | 1 | 0 | 1 | 7.1 | 6 | 7 | 3.90 | 3.70 | 3.79 |
| 348 | 16 | 0.0 | 16 | 15 | 0 | 1 | 0 | 1 | 6.3 | 7 | 8 | 3.66 | 3.45 | 3.55 |
| 349 | 17 | 5.9 | 16 | 14 | 0 | 2 | 0 | 2 | 12.5 | 4 | 10 | 3.85 | 3.64 | 3.70 |
| 350 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 3.69 | 3.46 | 3.61 |
| 351 | 17 | 0.0 | 17 | 17 | 0 | 0 | 0 | 0 | 0.0 | 3 | 14 | 3.63 | 3.50 | 3.52 |
| 352 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 7 | 8 | 4.06 | 3.88 | 3.96 |

NP - Not Pregnant
x - Excluded from summary statistics
[1] Nonviable fetus(es) excluded from summary statistics

**Individual Maternal Uterine Implantation Data and Average Fetal Body Weight Values**

| Group, Animal Number | Cor-pora Lutea | % Preim-plantation Loss | Implant Sites | Fetuses Viable | Fetuses Non-Viable[1] | Resorptions Early | Resorptions Late | Resorptions Total | % Postim-plantation Loss | Sex Male | Sex Female | Average Fetal Body Weight, g Male | Average Fetal Body Weight, g Female | Average Fetal Body Weight, g Litter |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | | | | | | | |
| 353 | 14 | 7.1 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 7 | 6 | 3.53 | 3.50 | 3.52 |
| 354 | 16 | 6.3 | 15 | 14 | 0 | 1 | 0 | 1 | 6.7 | 6 | 8 | 3.68 | 3.69 | 3.69 |
| 355 | 16 | 6.3 | 15 | 14 | 0 | 1 | 0 | 1 | 6.7 | 7 | 7 | 3.49 | 3.44 | 3.46 |
| 356 | 18 | 22.2 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 5 | 9 | 3.76 | 3.37 | 3.51 |
| 357 | 23 | 26.1 | 17 | 16 | 0 | 1 | 0 | 1 | 5.9 | 6 | 10 | 3.97 | 3.73 | 3.82 |
| 358 | 19 | 36.8 | 12 | 12 | 0 | 0 | 0 | 0 | 0.0 | 6 | 6 | 3.90 | 3.75 | 3.83 |
| 359 | 16 | 6.3 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 6 | 9 | 3.68 | 3.50 | 3.57 |
| 360 | 19 | 15.8 | 16 | 15 | 0 | 1 | 0 | 1 | 6.3 | 7 | 8 | 3.70 | 3.38 | 3.53 |
| 361 | 17 | 5.9 | 16 | 15 | 0 | 0 | 1 | 1 | 6.3 | 6 | 9 | 3.62 | 3.39 | 3.48 |
| 362 | 16 | 12.5 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 4.12 | 3.66 | 3.96 |
| 363 | 17 | 0.0 | 17 | 17 | 0 | 0 | 0 | 0 | 0.0 | 9 | 8 | 3.54 | 3.23 | 3.39 |
| 364 | 16 | 12.5 | 14 | 13 | 0 | 1 | 0 | 1 | 7.1 | 6 | 7 | 4.40 | 3.84 | 4.10 |
| 365 | 17 | 11.8 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 8 | 7 | 3.69 | 3.47 | 3.59 |
| 366 | 15 | 0.0 | 15 | 14 | 0 | 1 | 0 | 1 | 6.7 | 3 | 11 | 3.70 | 3.54 | 3.57 |
| 367 | 21 | 23.8 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 11 | 5 | 3.84 | 3.74 | 3.81 |
| 368 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 11 | 3 | 3.25 | 3.10 | 3.22 |
| 369 | 11 | 0.0 | 11 | 11 | 0 | 0 | 0 | 0 | 0.0 | 4 | 7 | 4.00 | 3.87 | 3.92 |
| 370 | 19 | 10.5 | 17 | 16 | 0 | 0 | 1 | 1 | 5.9 | 8 | 8 | 3.62 | 3.46 | 3.54 |
| 371 | 15 | 33.3 | 10 | 8 | 0 | 2 | 0 | 2 | 20.0 | 2 | 6 | 3.75 | 3.57 | 3.61 |
| 372 | 16 | 12.5 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 9 | 5 | 4.24 | 3.68 | 4.04 |
| 373 | 13 | 0.0 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 6 | 7 | 3.65 | 3.34 | 3.48 |
| 374 | 17 | 0.0 | 17 | 17 | 0 | 0 | 0 | 0 | 0.0 | 10 | 7 | 3.94 | 3.50 | 3.76 |
| 375 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 9 | 7 | 4.23 | 3.91 | 4.09 |
| 376 | 15 | 13.3 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 6 | 7 | 3.75 | 3.63 | 3.68 |
| 377 | 17 | 5.9 | 16 | 13 | 0 | 3 | 0 | 3 | 18.8 | 5 | 8 | 3.86 | 3.45 | 3.61 |
| 378 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 10 | 5 | 3.77 | 3.50 | 3.68 |

[1] Nonviable fetus(es) excluded from summary statistics

**Individual Maternal Uterine Implantation Data and Average Fetal Body Weight Values**

| Group, Animal Number | Corpora Lutea | % Preimplantation Loss | Implant Sites | Fetuses Viable | Fetuses Non-Viable[1] | Resorptions Early | Resorptions Late | Resorptions Total | % Postimplantation Loss | Sex Male | Sex Female | Average Fetal Body Weight, g Male | Average Fetal Body Weight, g Female | Average Fetal Body Weight, g Litter |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | | | | | | | |
| 379 | 13 | 0.0 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 9 | 4 | 3.78 | 3.63 | 3.73 |
| 380 | 18 | 33.3 | 12 | 11 | 0 | 1 | 0 | 1 | 8.3 | 5 | 6 | 3.90 | 3.83 | 3.86 |
| 381 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 9 | 6 | 3.67 | 3.52 | 3.61 |
| 382 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 1 | 13 | 3.70 | 3.63 | 3.64 |
| 383 | 19 | 0.0 | 19 | 17 | 0 | 2 | 0 | 2 | 10.5 | 9 | 8 | 3.62 | 3.41 | 3.52 |
| 384 | 19 | 31.6 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 5 | 8 | 4.46 | 4.09 | 4.23 |
| 385 | 15 | 0.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 10 | 5 | 4.21 | 4.04 | 4.15 |
| 386 | 25 | 20.0 | 20 | 20 | 0 | 0 | 0 | 0 | 0.0 | 12 | 8 | 3.77 | 3.66 | 3.73 |
| 387 | 14 | 0.0 | 14 | 14 | 0 | 0 | 0 | 0 | 0.0 | 5 | 9 | 4.08 | 3.63 | 3.79 |
| 388 | 13 | 0.0 | 13 | 13 | 0 | 0 | 0 | 0 | 0.0 | 3 | 10 | 4.47 | 4.31 | 4.35 |
| 389 | 16 | 6.3 | 15 | 12 | 0 | 3 | 0 | 3 | 20.0 | 4 | 8 | 3.55 | 3.59 | 3.57 |
| 390 | 20 | 25.0 | 15 | 15 | 0 | 0 | 0 | 0 | 0.0 | 6 | 9 | 3.67 | 3.46 | 3.54 |
| 391 | 13 | 0.0 | 13 | 10 | 0 | 3 | 0 | 3 | 23.1 | 4 | 6 | 4.10 | 3.95 | 4.01 |
| 392 | 22 | 27.3 | 16 | 14 | 0 | 2 | 0 | 2 | 12.5 | 7 | 7 | 3.44 | 3.44 | 3.44 |
| 393 | 11 | 0.0 | 11 | 11 | 0 | 0 | 0 | 0 | 0.0 | 5 | 6 | 4.72 | 4.43 | 4.56 |
| 394 | 18 | 44.4 | 10 | 9 | 0 | 1 | 0 | 1 | 10.0 | 3 | 6 | 3.93 | 3.78 | 3.83 |
| 395 | 16 | 0.0 | 16 | 14 | 0 | 1 | 1 | 2 | 12.5 | 5 | 9 | 3.70 | 3.54 | 3.60 |
| 396 | 20 | 5.0 | 19 | 18 | 0 | 1 | 0 | 1 | 5.3 | 11 | 7 | 3.61 | 3.46 | 3.55 |
| 397 x NP | | | | | | | | | | | | | | |
| 398 | 16 | 18.8 | 13 | 9 | 0 | 4 | 0 | 4 | 30.8 | 7 | 2 | 3.64 | 3.70 | 3.66 |
| 399 | 17 | 0.0 | 17 | 17 | 0 | 0 | 0 | 0 | 0.0 | 10 | 7 | 3.69 | 3.39 | 3.56 |
| 400 | 13 | 0.0 | 13 | 11 | 0 | 2 | 0 | 2 | 15.4 | 5 | 6 | 3.02 | 2.93 | 2.97 |
| 401 | 16 | 0.0 | 16 | 16 | 0 | 0 | 0 | 0 | 0.0 | 10 | 6 | 3.96 | 3.48 | 3.78 |
| 402 | 13 | 0.0 | 13 | 12 | 0 | 1 | 0 | 1 | 7.7 | 5 | 7 | 3.86 | 3.66 | 3.74 |
| 403 | 15 | 0.0 | 15 | 13 | 0 | 2 | 0 | 2 | 13.3 | 8 | 5 | 3.68 | 3.40 | 3.57 |
| 404 | 14 | 14.3 | 12 | 11 | 0 | 1 | 0 | 1 | 8.3 | 6 | 5 | 4.13 | 3.78 | 3.97 |

NP - Not Pregnant
x - Excluded from summary statistics
[1] Nonviable fetus(es) excluded from summary statistics

# APPENDIX K
Individual Animal Cesarean Section Data, Individual Fetal Body Weight Values, and Individual Crown Rump Distance Values

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 301 | | MSV | MVV | MSV | FVV | MSV / | FVV | MSV | MVV | MSV | MVV | FSV | MVV | FSV | FVV | | | | | | |
| | 6 / 9 | 3.6 | 3.6 | 3.8 | 4.0 | 3.7 | 3.7 | 3.6 | 3.8 | 3.5 | 3.8 | 3.8 | 3.8 | 3.8 | 3.3 | | | | | | |
| | | 36 | 35 | 37 | 37 | 36 | 35 | 35 | 37 | 36 | 36 | 37 | 36 | 37 | 35 | | | | | | |
| 302 | | MVV | MSV | FVV | MSV | FVV | MSV | FVV | MSV / | MVV | MSV | MVV | MSV | MVV | MSV | MVV | | | | | |
| | 8 / 8 | 3.3 | 3.7 | 3.4 | 3.7 | 3.1 | 3.1 | 3.2 | 3.5 | 3.2 | 3.3 | 3.6 | 3.7 | 3.6 | 3.5 | 3.2 | | | | | |
| | | 35 | 36 | 37 | 35 | 34 | 33 | 34 | 35 | 38 | 35 | 37 | 36 | 37 | 35 | 36 | | | | | |
| 303 | | MSV | MVV | E | MSV | FVV | FSV | FVV | MSV / | FVV | MSV | MVV | FSV | MVV | | | | | | | |
| | 8 / 5 | 3.3 | 3.8 | NA | 4.1 | 3.6 | 3.3 | 3.7 | 4.0 | 3.8 | 3.5 | 3.6 | 3.5 | 3.8 | | | | | | | |
| | | 35 | 37 | NA | 38 | 35 | 35 | 37 | 37 | 37 | 37 | 36 | 36 | 37 | | | | | | | |
| 304 | | FVV | FSV | MVV | FSV | MVV | MSV | FVV / | FSV | MVV | FSV | MVV | FSV | MVV | MSV | | | | | | |
| | 8 / 7 | 3.7 | 3.5 | 3.9 | 3.9 | 4.1 | 4.1 | 3.8 | 3.4 | 3.4 | 3.4 | 3.9 | 4.0 | 4.1 | 3.7 | | | | | | |
| | | 37 | 37 | 38 | 38 | 39 | 38 | 37 | 34 | 35 | 34 | 37 | 37 | 39 | 38 | | | | | | |
| 305 | | FSV | FVV | MSV | MVV | MSV | MVV | FSV | FVV / | MSV | FVV | MSV | MVV | MSV | MVV | MSV | | | | | |
| | 11 / 9 | 3.8 | 3.6 | 4.4 | 4.1 | 4.0 | 3.8 | 3.8 | 4.2 | 4.0 | 3.9 | 4.1 | 4.2 | 4.1 | 3.8 | 3.9 | | | | | |
| | | 37 | 37 | 40 | 37 | 38 | 37 | 36 | 38 | 38 | 38 | 39 | 38 | 39 | 38 | 39 | | | | | |
| 306 | | / FVV | FSV | | | | | | | | | | | | | | | | | | |
| | 3 / 7 | 6.4 | 7.0 | | | | | | | | | | | | | | | | | | |
| | | 45 | 46 | | | | | | | | | | | | | | | | | | |
| 307 | | FSV | MVV | MSV | MVV | FSV | MVV | FSV | MVV / | MSV | FVV | FSV | FVV | FSV | | | | | | | |
| | 8 / 5 | 3.1 | 3.7 | 4.0 | 3.7 | 3.3 | 3.9 | 3.4 | 3.5 | 3.7 | 3.5 | 3.7 | 3.8 | 3.2 | | | | | | | |
| | | 34 | 36 | 34 | 36 | 34 | 36 | 35 | 35 | 35 | 36 | 35 | 37 | 35 | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 308 | | FVV | FSV | MVV | FSV | MVV | FSV | FVV | MSV | FVV | FSV / MVV | | FSV | MVV | FSV | E | FVV | | | | |
| | 10 / 6 | 4.0 | 3.8 | 4.2 | 3.3 | 3.7 | 3.9 | 3.8 | 3.9 | 3.5 | 4.1 | 4.2 | 4.2 | 4.1 | 4.1 | NA | 3.7 | | | | |
| | | 37 | 35 | 38 | 37 | 35 | 37 | 37 | 38 | 34 | 37 | 36 | 38 | 40 | 39 | NA | 37 | | | | |
| 309 | | FSV | MVV | MSV | MVV | FSV | FVV | FSV | FVV | FSV / FVV | | FSV | | | | | | | | | |
| | 11 / 2 | 3.3 | 3.4 | 3.5 | 3.5 | 3.0 | 3.3 | 3.1 | 3.2 | 3.4 | 3.4 | 3.6 | | | | | | | | | |
| | | 34 | 34 | 36 | 35 | 35 | 35 | 35 | 36 | 34 | 34 | 38 | | | | | | | | | |
| 310 | | MVV | FSV | FVV | E | MSV / FVV | | FSV | E | FVV | MSV | FVV | FSV | MVV | FSV | FVV | MSV | FVV | | | |
| | 7 / 13 | 3.8 | 3.9 | 3.9 | NA | 3.9 | 3.8 | 3.7 | NA | 3.7 | 4.2 | 4.1 | 4.0 | 3.9 | 3.7 | 3.8 | 3.7 | 3.8 | | | |
| | | 35 | 36 | 35 | NA | 35 | 36 | 34 | NA | 38 | 35 | 37 | 37 | 36 | 35 | 35 | 37 | 35 | | | |
| 311 | | MSV | MVV | FSV / MVV | | FSV | MVV | FSV | FVV | MSV | FVV | FSV | FVV | MSV | MVV | E | MSV | E | | | |
| | 3 / 14 | 3.5 | 3.7 | 3.5 | 3.6 | 3.2 | 3.5 | 3.2 | 3.3 | 3.5 | 3.3 | 3.6 | 3.5 | 3.7 | 3.6 | NA | 3.6 | NA | | | |
| | | 36 | 34 | 37 | 33 | 36 | 36 | 34 | 35 | 38 | 35 | 37 | 36 | 38 | 37 | NA | 38 | NA | | | |
| 312 | | MVV | MSV | FVV | FSV | MVV | FSV / MVV | | MSV | MVV | FSV | MVV | MSV | MVV | MSV | FVV | FSV | FVV | | | |
| | 6 / 11 | 3.3 | 3.7 | 3.3 | 3.3 | 3.5 | 3.1 | 3.6 | 3.5 | 3.7 | 3.2 | 3.5 | 3.8 | 2.1 | 3.3 | 3.0 | 3.1 | 3.0 | | | |
| | | 33 | 35 | 36 | 35 | 35 | 34 | 39 | 38 | 37 | 37 | 37 | 36 | 29 | 35 | 35 | 35 | 34 | | | |
| 313 | | MSV | FVV | FSV | FVV | FSV | FVV / FSV | | MVV | FSV | FVV | FSV | FVV | MSV | MVV | | | | | | |
| | 8 / 10 | 3.7 | 3.2 | 3.5 | 3.5 | 3.6 | 3.4 | 3.1 | 3.5 | 3.4 | 3.4 | 3.8 | 3.5 | 3.5 | 3.6 | | | | | | |
| | | 36 | 37 | 38 | 37 | 35 | 36 | 32 | 35 | 36 | 36 | 39 | 38 | 37 | 36 | | | | | | |
| 314 | NP | | | | | | | | | | | | | | | | | | | | |
| 315 | | MSV | MVV | FSV | FVV | MSV | MVV / MSV | | MVV | MSV | FVV | FSV | FVV | FSV | MVV | | | | | | |
| | 9 / 12 | 3.9 | 3.5 | 3.9 | 4.2 | 3.7 | 3.6 | 3.9 | 3.9 | 4.0 | 3.7 | 3.8 | 3.6 | 3.8 | 3.7 | | | | | | |
| | | 38 | 36 | 38 | 37 | 34 | 37 | 36 | 37 | 37 | 37 | 38 | 37 | 35 | 36 | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right) NP - Not Pregnant
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 316 | | FSV | MVV | MSV | MVV | MSV / | FVV | FSV | MVV | FSV | FVV | FSV | FVV | L | | | | | | | |
| | 7 / 10 | 3.0 | 3.2 | 2.9 | 3.2 | 2.9 | 2.7 | 2.6 | 2.9 | 2.4 | 3.2 | 3.1 | 3.1 | NA | | | | | | | |
| | | 31 | 34 | 33 | 32 | 33 | 31 | 31 | 32 | 30 | 32 | 32 | 32 | NA | | | | | | | |
| 317 | | FVV | MSV | FVV | MSV | MVV | MSV / | MVV | FSV | MVV | MSV | MVV | FSV | MVV | FSV | MVV | MSV | | | | |
| | 6 / 10 | 3.0 | 3.5 | 3.5 | 3.8 | 3.8 | 3.3 | 3.5 | 2.7 | 3.9 | 3.7 | 3.9 | 3.6 | 3.7 | 3.7 | 3.5 | 3.6 | | | | |
| | | 31 | 33 | 33 | 35 | 34 | 32 | 33 | 30 | 36 | 36 | 32 | 34 | 32 | 34 | 33 | 35 | | | | |
| 318 | | MSV | MVV | MSV | E | MVV / | MSV | FVV | FSV | FVV | MSV | E | MVV | E | MSV | | | | | | |
| | 5 / 9 | 3.6 | 3.4 | 3.9 | NA | 3.9 | 3.9 | 3.7 | 3.2 | 3.8 | 3.8 | NA | 3.9 | NA | 3.5 | | | | | | |
| | | 33 | 32 | 34 | NA | 34 | 33 | 33 | 31 | 32 | 33 | NA | 33 | NA | 34 | | | | | | |
| 319 | | FVV | E | FSV | MVV | MSV | MVV | FSV / | MVV | FSV | FVV | MSV | FVV | MSV | MVV | MSV | FVV | MSV | MVV | | |
| | 7 / 11 | 3.8 | NA | 3.9 | 3.9 | 3.7 | 4.1 | 3.7 | 4.2 | 3.6 | 3.6 | 3.8 | 4.0 | 4.1 | 4.3 | 4.1 | 3.5 | 4.0 | 4.1 | | |
| | | 35 | NA | 35 | 35 | 35 | 35 | 34 | 34 | 33 | 35 | 34 | 33 | 34 | 34 | 35 | 34 | 34 | 36 | | |
| 320 | | FVV | FSV | MVV | FSV | MVV | FSV / | MVV | MSV | FVV | FSV | MVV | MSV | FVV | | | | | | | |
| | 7 / 8 | 3.2 | 3.3 | 4.2 | 3.4 | 4.2 | 3.5 | 3.9 | 3.4 | 3.8 | 3.4 | 3.4 | 4.0 | 3.5 | | | | | | | |
| | | 33 | 32 | 34 | 34 | 35 | 33 | 33 | 31 | 34 | 34 | 32 | 35 | 33 | | | | | | | |
| 321 | | MSV | MVV | FSV | FVV | MSV | MVV / | MSV | MVV | MSV | MVV | FSV | FVV | FSV | MVV | | | | | | |
| | 6 / 8 | 3.6 | 3.6 | 3.5 | 3.3 | 3.4 | 3.3 | 3.0 | 3.0 | 3.4 | 3.6 | 3.2 | 3.2 | 3.3 | 3.2 | | | | | | |
| | | 36 | 35 | 36 | 33 | 34 | 34 | 33 | 33 | 35 | 34 | 33 | 34 | 33 | 32 | | | | | | |
| 322 | | FSV | MVV | MSV | FVV / | MSV | FVV | FSV | FVV | MSV | MVV | FSV | FVV | MSV | FVV | | | | | | |
| | 4 / 10 | 3.8 | 3.9 | 4.5 | 4.3 | 3.9 | 3.3 | 4.0 | 3.5 | 4.4 | 4.1 | 4.0 | 3.8 | 3.9 | 2.8 | | | | | | |
| | | 36 | 36 | 42 | 37 | 41 | 34 | 39 | 38 | 36 | 38 | 37 | 36 | 36 | 34 | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption L - Late Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 323 | | MVV | FSV | MVV | FSV | FVV | MSV / | MVV | FSV | FVV | MSV | MVV | MSV | MVV | FSV | MVV | FSV | FVV | L | | |
| | 7 / 13 | 3.5 | 3.6 | 3.9 | 2.8 | 3.6 | 3.9 | 3.6 | 3.5 | 3.8 | 4.3 | 4.3 | 4.3 | 4.1 | 3.9 | 4.1 | 3.7 | 3.6 | NA | | |
| | | 36 | 35 | 37 | 35 | 37 | 37 | 33 | 35 | 34 | 34 | 37 | 35 | 34 | 37 | 35 | 36 | 35 | NA | | |
| 324 | | FSV | FVV | MSV | FVV | MSV | FVV | MSV | MVV | MSV | FVV | FSV | E | / MVV | MSV | FVV | MSV | | | | |
| | 12 / 4 | 3.3 | 3.6 | 3.6 | 3.7 | 3.3 | 3.7 | 3.9 | 3.7 | 3.6 | 3.6 | 3.4 | NA | 3.7 | 3.8 | 3.2 | 3.6 | | | | |
| | | 32 | 35 | 36 | 36 | 36 | 35 | 36 | 37 | 38 | 35 | 36 | NA | 38 | 37 | 36 | 37 | | | | |
| 325 | | FVV | MSV | MVV | FSV | MVV | MSV | FVV / | FSV | FVV | MSV | MVV | MSV | FVV | FSV | FVV | MSV | | | | |
| | 7 / 9 | 3.1 | 3.7 | 3.8 | 3.7 | 3.5 | 3.7 | 3.6 | 3.8 | 3.2 | 3.6 | 3.8 | 3.8 | 4.0 | 3.5 | 3.2 | 3.3 | | | | |
| | | 35 | 34 | 34 | 35 | 34 | 35 | 33 | 35 | 33 | 34 | 34 | 36 | 34 | 34 | 32 | 35 | | | | |
| 326 | | MSV | FVV | FSV | FVV | FSV | MVV | FSV / | FVV | FSV | FVV | FSV | FVV | FSV | FVV | FSV | | | | | |
| | 7 / 8 | 4.1 | 3.7 | 3.6 | 3.7 | 3.7 | 3.8 | 3.4 | 3.4 | 3.2 | 3.3 | 4.1 | 3.8 | 4.0 | 3.9 | 3.7 | | | | | |
| | | 35 | 34 | 34 | 34 | 35 | 35 | 32 | 33 | 34 | 33 | 36 | 37 | 34 | 35 | 33 | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption L - Late Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 327 | | FVV | MSV | FVV | MSV | FVV | MSV | MVV | MSV | MVV / | MSV | MVV | MSV | | | | | | | | |
| | 10 / 4 | 3.1 | 3.3 | 3.7 | 3.5 | 3.6 | 3.7 | 3.7 | 3.7 | 3.5 | 4.0 | 3.7 | 3.8 | | | | | | | | |
| | | 34 | 36 | 35 | 37 | 36 | 37 | 37 | 36 | 35 | 38 | 38 | 35 | | | | | | | | |
| 328 | | MSV | FVV | MSV | MVV | MSV | MVV / | FSV | FVV | MSV | MVV | MSV | FVV | MSV | FVV | MSV | FVV | | | | |
| | 6 / 10 | 3.6 | 3.8 | 3.9 | 3.9 | 4.0 | 3.8 | 3.3 | 3.4 | 3.8 | 3.6 | 4.2 | 3.8 | 3.8 | 3.4 | 3.3 | 3.3 | | | | |
| | | 35 | 38 | 37 | 38 | 39 | 37 | 37 | 36 | 38 | 38 | 39 | 35 | 36 | 37 | 36 | 34 | | | | |
| 329 | | FVV | MSV | MVV | MSV | MVV / | MSV | MVV | MSV | MVV | MSV | MVV | FSV | E | FVV | FSV | | | | | |
| | 5 / 10 | 3.9 | 4.2 | 4.2 | 4.2 | 3.9 | 2.4 | 3.8 | 3.9 | 4.1 | 4.0 | 4.1 | 3.8 | NA | 3.9 | 3.4 | | | | | |
| | | 36 | 37 | 39 | 37 | 37 | 31 | 37 | 38 | 37 | 37 | 37 | 36 | NA | 36 | 35 | | | | | |
| 330 | | E | MSV | MVV | FSV | FVV | FSV | MVV | MSV / | E | FVV | FSV | FVV | FSV | MVV | FSV | MVV | MSV | | | |
| | 8 / 9 | NA | 3.6 | 3.9 | 3.7 | 3.8 | 3.8 | 3.6 | 3.9 | NA | 3.5 | 3.5 | 3.8 | 3.7 | 3.9 | 3.7 | 3.7 | 3.3 | | | |
| | | NA | 36 | 36 | 35 | 37 | 35 | 36 | 36 | NA | 37 | 37 | 36 | 37 | 37 | 34 | 37 | 36 | | | |
| 331 | | FVV | FSV | FVV | FSV | MVV | MSV | FVV | FSV / | MVV | FSV | FVV | FSV | FVV | | | | | | | |
| | 8 / 5 | 3.2 | 3.6 | 3.5 | 3.4 | 3.6 | 3.7 | 3.4 | 3.3 | 3.5 | 3.3 | 3.5 | 3.6 | 3.5 | | | | | | | |
| | | 32 | 36 | 36 | 36 | 37 | 37 | 36 | 35 | 38 | 36 | 35 | 35 | 36 | | | | | | | |
| 332 | | FSV | MVV | MSV | FVV | MSV | FVV / | MSV | FVV | MSV | FVV | MSV | MVV | MSV | FVV | MSV | MVV | | | | |
| | 7 / 10 | 3.5 | 3.5 | 3.7 | 3.2 | 3.6 | 3.4 | 3.8 | 3.4 | 3.3 | 3.3 | 3.6 | 3.6 | 3.7 | 3.4 | 3.4 | 3.4 | | | | |
| | | 37 | 37 | 36 | 35 | 33 | 34 | 36 | 35 | 34 | 34 | 36 | 37 | 35 | 34 | 34 | 35 | | | | |
| 333 | | MVV | E | MSV / | FVV | E | FSV | MVV | MSV | MVV | MSV | MVV | FSV | FVV | | | | | | | |
| | 5 / 13 | 3.4 | NA | 3.8 | 3.7 | NA | 3.4 | 3.5 | 3.5 | 3.8 | 3.5 | 3.7 | 3.3 | 3.3 | | | | | | | |
| | | 35 | NA | 35 | 35 | NA | 35 | 36 | 35 | 34 | 36 | 36 | 38 | 37 | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 334 | | FVV | MSV | MVV | FSV | MVV | FSV | FVV / | MSV | FVV | MSV | MVV | E | FSV | MVV | MSV | FVV | | | | |
| | 7 / 9 | 3.3 | 3.3 | 3.8 | 3.4 | 3.3 | 3.6 | 3.3 | 3.6 | 3.1 | 3.7 | 3.7 | NA | 3.3 | 3.9 | 3.8 | 3.2 | | | | |
| | | 35 | 36 | 37 | 35 | 35 | 37 | 33 | 37 | 35 | 37 | 37 | NA | 34 | 38 | 37 | 34 | | | | |
| 335 | | MSV | MVV | FSV | FVV | MSV / | FVV | FSV | MVV | FSV | FVV | MSV | FVV | MSV | FVV | MSV | MVV | | | | |
| | 5 / 11 | 3.5 | 3.4 | 3.5 | 3.7 | 3.6 | 3.4 | 3.3 | 3.7 | 3.7 | 3.6 | 2.9 | 3.6 | 3.8 | 3.7 | 3.5 | 3.1 | | | | |
| | | 37 | 36 | 35 | 36 | 35 | 36 | 37 | 38 | 38 | 38 | 33 | 37 | 37 | 36 | 37 | 34 | | | | |
| 336 | | E | FVV | MSV | FVV | MSV | FVV / | FSV | MVV | MSV | MVV | MSV | FVV | E | | | | | | | |
| | 6 / 7 | NA | 4.3 | 4.3 | 4.0 | 4.4 | 4.4 | 4.2 | 4.4 | 4.2 | 4.4 | 4.5 | 4.4 | NA | | | | | | | |
| | | NA | 40 | 39 | 37 | 38 | 38 | 37 | 38 | 39 | 39 | 40 | 38 | NA | | | | | | | |
| 337 | | MSV | MVV | MSV | MVV | FSV | FVV / | MSV | MVV | FSV | MVV | | | | | | | | | | |
| | 8 / 6 | 3.7 | 3.3 | 4.0 | 3.1 | 3.4 | 3.4 | 3.2 | 3.4 | 3.4 | 2.8 | | | | | | | | | | |
| | | 36 | 34 | 36 | 33 | 34 | 34 | 35 | 32 | 34 | 33 | | | | | | | | | | |
| 338 | | FVV | MSV / | | | | | | | | | | | | | | | | | | |
| | 2 / 4 | 3.9 | 4.8 | | | | | | | | | | | | | | | | | | |
| | | 37 | 38 | | | | | | | | | | | | | | | | | | |
| 339 | | MSV | FVV | FSV | FVV / | MSV | MVV | FSV | FVV | FSV | MVV | FSV | FVV | FSV | FVV | | | | | | |
| | 5 / 10 | 3.9 | 4.0 | 3.7 | 4.4 | 4.1 | 3.8 | 3.7 | 4.0 | 4.2 | 4.1 | 3.6 | 3.8 | 3.6 | 3.5 | | | | | | |
| | | 39 | 37 | 36 | 37 | 39 | 38 | 35 | 37 | 36 | 38 | 35 | 37 | 33 | 35 | | | | | | |
| 340 | NP | | | | | | | | | | | | | | | | | | | | |
| 341 | | FSV | FVV | MSV | FVV | FSV | FVV / | MSV | FVV | MSV | FVV | E | FSV | | | | | | | | |
| | 7 / 6 | 3.6 | 3.6 | 3.9 | 3.2 | 3.0 | 3.3 | 3.6 | 3.3 | 3.7 | 3.7 | NA | 3.6 | | | | | | | | |
| | | 36 | 35 | 36 | 36 | 34 | 34 | 35 | 37 | 37 | 35 | NA | 38 | | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right) NP - Not Pregnant
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 342 | | FVV | FSV | MVV | FSV | MVV | MSV | MVV / | FSV | MVV | MSV | MVV | FSV | FVV | | | | | | | |
| | 7 / 7 | 3.6 | 3.4 | 3.8 | 3.9 | 3.8 | 3.4 | 3.2 | 3.6 | 3.6 | 3.7 | 4.1 | 3.8 | 3.3 | | | | | | | |
| | | 35 | 34 | 33 | 35 | 35 | 34 | 34 | 35 | 34 | 35 | 36 | 36 | 32 | | | | | | | |
| 343 | | MSV | MVV | FSV | FVV | FSV | FVV | MSV | FVV | MSV / | FVV | MSV | FVV | MSV | MVV | FSV | | | | | |
| | 9 / 6 | 3.9 | 3.5 | 3.8 | 3.2 | 3.8 | 3.3 | 3.7 | 3.6 | 3.9 | 2.5 | 4.0 | 2.5 | 4.0 | 3.9 | 3.4 | | | | | |
| | | 34 | 35 | 34 | 33 | 35 | 32 | 33 | 35 | 35 | 29 | 34 | 29 | 36 | 34 | 35 | | | | | |
| 344 | | FVV | MSV | FVV | FSV | FVV | MSV | MVV | MSV | MVV / | MSV | MVV | FSV | FVV | MSV | | | | | | |
| | 10 / 7 | 3.5 | 3.9 | 4.0 | 3.5 | 3.8 | 4.0 | 3.7 | 3.7 | 3.7 | 3.7 | 3.8 | 3.4 | 3.7 | 3.4 | | | | | | |
| | | 32 | 37 | 33 | 32 | 36 | 35 | 34 | 34 | 34 | 34 | 35 | 34 | 34 | 33 | | | | | | |
| 345 | | FSV | FVV | MSV | FVV | FSV | MVV | MSV | FVV | FSV / | | | | | | | | | | | |
| | 9 / 6 | 3.5 | 3.6 | 3.8 | 3.6 | 3.6 | 4.0 | 4.2 | 3.6 | 3.9 | | | | | | | | | | | |
| | | 37 | 33 | 36 | 34 | 35 | 37 | 36 | 36 | 34 | | | | | | | | | | | |
| 346 | | MVV | MSV | MVV | FSV | MVV | MSV | MVV / | FSV | FVV | MSV | FVV | FSV | MVV | MSV | | | | | | |
| | 7 / 7 | 3.8 | 4.1 | 4.0 | 4.0 | 4.5 | 4.0 | 4.1 | 3.8 | 3.9 | 4.0 | 4.0 | 4.1 | 4.2 | 3.5 | | | | | | |
| | | 36 | 34 | 34 | 33 | 35 | 34 | 35 | 34 | 33 | 36 | 37 | 36 | 37 | 35 | | | | | | |
| 347 | | E | MSV | FVV | FSV | FVV | MSV | FVV | MSV / | FVV | FSV | FVV | MSV | MVV | MSV | | | | | | |
| | 8 / 7 | NA | 4.0 | 3.8 | 3.5 | 3.6 | 3.7 | 3.8 | 4.2 | 3.8 | 3.8 | 3.6 | 4.1 | 3.8 | 3.6 | | | | | | |
| | | NA | 35 | 35 | 35 | 32 | 32 | 35 | 38 | 33 | 35 | 35 | 36 | 35 | 33 | | | | | | |
| 348 | | FVV | MSV | FVV | FSV | E | MVV | MSV | MVV | FSV / | FVV | MSV | FVV | MSV | MVV | FSV | FVV | | | | |
| | 9 / 7 | 3.4 | 3.8 | 3.4 | 3.6 | NA | 3.6 | 3.5 | 3.5 | 3.3 | 3.5 | 3.4 | 3.5 | 4.0 | 3.8 | 3.5 | 3.4 | | | | |
| | | 36 | 35 | 35 | 35 | NA | 36 | 35 | 34 | 36 | 36 | 35 | 35 | 37 | 37 | 36 | 37 | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 349 | | MSV | FVV | MSV | E | FVV / | FSV | FVV | FSV | FVV | FSV | E | FVV | MSV | MVV | FSV | FVV | | | | |
| | 5 / 12 | 3.6 | 3.8 | 4.0 | NA | 3.6 | 3.4 | 3.3 | 3.5 | 3.9 | 3.7 | NA | 3.9 | 3.8 | 4.0 | 3.7 | 3.6 | | | | |
| | | 38 | 37 | 36 | NA | 35 | 37 | 35 | 34 | 34 | 35 | NA | 36 | 34 | 35 | 35 | 36 | | | | |
| 350 | | MVV | FSV | FVV | MSV | MVV / | MSV | MVV | MSV | MVV | MSV | FVV | FSV | MVV | FSV | | | | | | |
| | 5 / 9 | 3.4 | 3.5 | 3.7 | 3.7 | 3.6 | 3.9 | 3.4 | 3.8 | 4.2 | 3.8 | 3.5 | 3.6 | 3.4 | 3.0 | | | | | | |
| | | 36 | 35 | 36 | 35 | 38 | 37 | 36 | 37 | 39 | 38 | 38 | 37 | 35 | 37 | | | | | | |
| 351 | | FSV | MVV | FSV | FVV | FSV | FVV | FSV / | FVV | FSV | FVV | FSV | FVV | FSV | FVV | MSV | FVV | MSV | | | |
| | 7 / 10 | 3.2 | 3.7 | 3.4 | 3.4 | 3.6 | 3.8 | 3.5 | 3.3 | 3.5 | 3.4 | 3.8 | 3.7 | 3.7 | 3.6 | 3.7 | 3.1 | 3.5 | | | |
| | | 32 | 33 | 31 | 32 | 35 | 34 | 34 | 33 | 33 | 34 | 36 | 37 | 36 | 35 | 33 | 33 | 32 | | | |
| 352 | | FVV | FSV | FVV | FSV | FVV | MSV | FVV / | MSV | MVV | MSV | FVV | MSV | MVV | MSV | FVV | | | | | |
| | 7 / 8 | 3.4 | 3.9 | 3.9 | 4.0 | 3.7 | 3.9 | 4.1 | 4.3 | 3.7 | 4.1 | 4.2 | 4.2 | 4.2 | 4.0 | 3.8 | | | | | |
| | | 33 | 35 | 34 | 36 | 33 | 34 | 37 | 36 | 33 | 35 | 35 | 36 | 37 | 37 | 35 | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 353 | | FSV | MVV | MSV | FVV | MSV | MVV | FSV / | MVV | MSV | FVV | FSV | FVV | MSV | | | | | | | |
| | 7 / 7 | 3.5 | 3.7 | 3.6 | 3.5 | 3.6 | 3.4 | 3.5 | 3.6 | 3.5 | 3.7 | 3.4 | 3.4 | 3.3 | | | | | | | |
| | | 38 | 36 | 36 | 36 | 37 | 36 | 35 | 37 | 37 | 36 | 35 | 35 | 35 | | | | | | | |
| 354 | | MVV | FSV | FVV | FSV | FVV / | MSV | MVV | FSV | FVV | E | FSV | FVV | MSV | MVV | MSV | | | | | |
| | 6 / 10 | 3.8 | 3.7 | 3.8 | 3.4 | 3.6 | 3.5 | 3.5 | 3.8 | 3.5 | NA | 3.8 | 3.9 | 3.9 | 3.8 | 3.6 | | | | | |
| | | 37 | 39 | 37 | 32 | 35 | 36 | 36 | 36 | 35 | NA | 36 | 36 | 36 | 37 | 37 | | | | | |
| 355 | | FSV | FVV | E | MSV / | MVV | MSV | MVV | MSV | FVV | FSV | MVV | MSV | FVV | FSV | FVV | | | | | |
| | 5 / 11 | 3.2 | 3.4 | NA | 3.6 | 3.4 | 3.5 | 3.5 | 3.6 | 3.6 | 3.4 | 3.3 | 3.5 | 3.4 | 3.6 | 3.5 | | | | | |
| | | 36 | 35 | NA | 36 | 35 | 36 | 36 | 35 | 36 | 36 | 34 | 36 | 35 | 36 | 34 | | | | | |
| 356 | | FVV | MSV | MVV | FSV | FVV | FSV / | MVV | MSV | FVV | FSV | FVV | FSV | MVV | FSV | | | | | | |
| | 8 / 10 | 3.6 | 4.0 | 4.1 | 3.5 | 3.2 | 3.4 | 3.5 | 3.5 | 3.4 | 3.4 | 3.5 | 3.3 | 3.7 | 3.0 | | | | | | |
| | | 36 | 38 | 39 | 36 | 34 | 36 | 37 | 36 | 34 | 35 | 35 | 34 | 36 | 34 | | | | | | |
| 357 | | FSV | FVV | MSV | MVV | MSV / | FVV | FSV | FVV | E | MSV | MVV | MSV | FVV | FSV | FVV | FSV | FVV | | | |
| | 8 / 15 | 3.9 | 4.1 | 4.1 | 4.0 | 3.8 | 3.8 | 3.9 | 3.8 | NA | 3.9 | 4.1 | 3.9 | 4.1 | 4.1 | 4.0 | 3.1 | 2.5 | | | |
| | | 36 | 37 | 39 | 36 | 36 | 37 | 37 | 38 | NA | 37 | 38 | 34 | 35 | 36 | 36 | 32 | 32 | | | |
| 358 | | FVV | FSV | MVV / | FSV | FVV | MSV | MVV | MSV | MVV | MSV | FVV | FSV | | | | | | | | |
| | 8 / 11 | 3.7 | 4.1 | 3.9 | 3.9 | 3.5 | 3.7 | 4.0 | 3.9 | 3.9 | 4.0 | 3.7 | 3.6 | | | | | | | | |
| | | 35 | 38 | 39 | 36 | 35 | 35 | 37 | 37 | 36 | 38 | 38 | 36 | | | | | | | | |
| 359 | | MSV | FVV | FSV | MVV | FSV | FVV | MSV | FVV / | FSV | MVV | MSV | FVV | MSV | FVV | FSV | | | | | |
| | 8 / 8 | 3.4 | 3.5 | 3.6 | 3.8 | 3.6 | 3.3 | 3.6 | 3.7 | 3.4 | 3.8 | 3.7 | 3.7 | 3.8 | 3.4 | 3.3 | | | | | |
| | | 37 | 35 | 35 | 38 | 37 | 36 | 38 | 38 | 35 | 38 | 39 | 38 | 38 | 35 | 37 | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 360 | | MSV | FVV | FSV | MVV | MSV | FVV | FSV | FVV | FSV / | E | FVV | MSV | MVV | MSV | MVV | FSV | | | | |
| | 11 / 8 | 3.4 | 3.2 | 3.3 | 3.8 | 3.6 | 3.6 | 3.4 | 3.5 | 3.4 | NA | 3.4 | 3.9 | 3.9 | 3.7 | 3.6 | 3.2 | | | | |
| | | 38 | 36 | 35 | 37 | 36 | 38 | 36 | 37 | 36 | NA | 34 | 38 | 39 | 36 | 38 | 36 | | | | |
| 361 | | MVV | MSV | FVV | MSV | FVV | FSV | L / | FVV | FSV | FVV | MSV | FVV | MSV | FVV | MSV | FVV | | | | |
| | 7 / 10 | 3.3 | 4.0 | 3.5 | 3.5 | 3.6 | 3.5 | NA | 3.2 | 3.1 | 3.3 | 3.6 | 3.4 | 3.7 | 3.3 | 3.6 | 3.6 | | | | |
| | | 36 | 37 | 38 | 35 | 35 | 35 | NA | 36 | 34 | 36 | 37 | 35 | 35 | 34 | 35 | 36 | | | | |
| 362 | | MSV | FVV | MSV | MVV | MSV | MVV | FSV / | FVV | FSV | MVV | MSV | MVV | MSV | FVV | | | | | | |
| | 7 / 9 | 3.9 | 3.5 | 4.2 | 4.0 | 4.1 | 4.2 | 4.0 | 3.5 | 3.7 | 4.1 | 4.1 | 4.3 | 4.2 | 3.6 | | | | | | |
| | | 39 | 37 | 38 | 36 | 37 | 38 | 37 | 34 | 37 | 37 | 38 | 38 | 37 | 36 | | | | | | |
| 363 | | FVV | FSV | MVV | MSV | MVV | MSV | MVV / | FSV | FVV | FSV | FVV | FSV | MVV | MSV | MVV | FSV | MVV | | | |
| | 7 / 10 | 3.4 | 3.4 | 3.5 | 3.4 | 3.8 | 3.6 | 3.5 | 2.9 | 3.2 | 3.2 | 3.1 | 3.5 | 3.5 | 3.7 | 3.6 | 3.1 | 3.3 | | | |
| | | 36 | 35 | 37 | 35 | 36 | 36 | 36 | 34 | 36 | 34 | 35 | 36 | 37 | 37 | 37 | 34 | 34 | | | |
| 364 | | FSV | FVV | FSV | FVV | FSV / | MVV | MSV | MVV | MSV | MVV | FSV | E | MVV | FSV | | | | | | |
| | 6 / 10 | 4.1 | 4.1 | 4.2 | 2.6 | 3.7 | 4.3 | 4.1 | 4.6 | 4.5 | 4.4 | 4.4 | NA | 4.5 | 3.8 | | | | | | |
| | | 38 | 40 | 39 | 35 | 37 | 37 | 36 | 39 | 38 | 36 | 39 | NA | 39 | 37 | | | | | | |
| 365 | | FVV | FSV | FVV | MSV | FVV | MSV | MVV | MSV | FVV / | MSV | FVV | MSV | FVV | MSV | MVV | | | | | |
| | 10 / 7 | 3.6 | 3.0 | 3.4 | 3.7 | 3.5 | 3.6 | 3.7 | 3.4 | 3.7 | 3.9 | 3.5 | 3.9 | 3.6 | 3.5 | 3.8 | | | | | |
| | | 35 | 36 | 35 | 37 | 36 | 37 | 37 | 34 | 34 | 38 | 37 | 37 | 35 | 35 | 37 | | | | | |
| 366 | | E | FSV | FVV | FSV | FVV / | FSV | MVV | MSV | MVV | FSV | FVV | FSV | FVV | FSV | FVV | | | | | |
| | 5 / 10 | NA | 3.8 | 3.7 | 3.3 | 3.8 | 3.4 | 3.3 | 3.8 | 4.0 | 3.7 | 3.3 | 3.6 | 3.8 | 3.3 | 3.2 | | | | | |
| | | NA | 37 | 36 | 34 | 37 | 34 | 32 | 36 | 36 | 36 | 36 | 37 | 35 | 33 | 37 | | | | | |

SEX CODES: M - Male F - Female NA - Not Applicable/Not Available
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption L - Late Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 367 | | MVV | FSV | FVV | MSV | MVV | FSV | MVV | MSV | MVV / | MSV | MVV | FSV | MVV | MSV | MVV | FSV | | | | |
| | 12 / 9 | 4.0 | 3.6 | 3.5 | 4.0 | 4.0 | 3.7 | 3.7 | 3.5 | 3.6 | 3.7 | 3.8 | 3.9 | 3.9 | 4.1 | 3.9 | 4.0 | | | | |
| | | 38 | 36 | 37 | 34 | 37 | 35 | 37 | 34 | 37 | 35 | 36 | 39 | 37 | 37 | 34 | 41 | | | | |
| 368 | | MSV | MVV | FSV | MVV | MSV | MVV / | FSV | MVV | FSV | MVV | MSV | MVV | MSV | MVV | | | | | | |
| | 6 / 8 | 3.0 | 3.1 | 3.1 | 3.4 | 3.4 | 2.8 | 2.8 | 3.4 | 3.4 | 3.5 | 3.5 | 3.6 | 3.1 | 3.0 | | | | | | |
| | | 31 | 34 | 31 | 34 | 35 | 31 | 33 | 33 | 34 | 33 | 33 | 34 | 31 | 33 | | | | | | |
| 369 | | FVV | MSV | MVV | FSV | MVV | FSV | FVV | MSV | FVV / | FSV | FVV | | | | | | | | | |
| | 9 / 2 | 3.7 | 4.2 | 4.0 | 3.8 | 4.0 | 3.9 | 3.9 | 3.8 | 3.8 | 4.1 | 3.9 | | | | | | | | | |
| | | 34 | 32 | 33 | 35 | 35 | 33 | 33 | 34 | 33 | 34 | 35 | | | | | | | | | |
| 370 | | FSV | MVV | MSV | FVV | MSV | FVV | MSV / | MVV | FSV | L | MVV | MSV | FVV | MSV | FVV | FSV | FVV | | | |
| | 8 / 11 | 3.3 | 3.9 | 3.6 | 3.8 | 3.6 | 3.6 | 3.1 | 3.3 | 2.9 | NA | 4.0 | 4.1 | 4.0 | 3.4 | 3.7 | 3.2 | 3.2 | | | |
| | | 30 | 34 | 31 | 34 | 33 | 33 | 31 | 33 | 33 | NA | 34 | 34 | 35 | 32 | 33 | 32 | 33 | | | |
| 371 | | FVV | E | FSV | FVV | FSV | FVV | E | MSV | MVV | FSV / | | | | | | | | | | |
| | 10 / 5 | 3.1 | NA | 3.6 | 3.8 | 3.5 | 3.5 | NA | 3.7 | 3.8 | 3.9 | | | | | | | | | | |
| | | 32 | NA | 32 | 35 | 34 | 36 | NA | 34 | 35 | 35 | | | | | | | | | | |
| 372 | | FSV | MVV | MSV | MVV | MSV | MVV | FSV / | MVV | MSV | FVV | FSV | MVV | MSV | FVV | | | | | | |
| | 9 / 7 | 3.8 | 4.4 | 4.0 | 4.3 | 4.5 | 4.3 | 4.2 | 4.2 | 4.2 | 4.2 | 4.0 | 4.3 | 4.0 | 2.2 | | | | | | |
| | | 35 | 35 | 37 | 33 | 35 | 36 | 35 | 38 | 37 | 37 | 38 | 37 | 37 | 29 | | | | | | |
| 373 | | MSV | FVV | FSV | MVV | MSV / | FVV | MSV | FVV | FSV | MVV | FSV | MVV | FSV | | | | | | | |
| | 5 / 8 | 3.3 | 3.3 | 3.2 | 3.4 | 3.8 | 3.4 | 3.8 | 3.1 | 3.5 | 3.7 | 3.6 | 3.9 | 3.3 | | | | | | | |
| | | 34 | 36 | 35 | 35 | 39 | 35 | 39 | 34 | 37 | 35 | 37 | 36 | 38 | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption L - Late Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 374 | | FVV | FSV | FVV | FSV | MVV | MSV | MVV | FSV | MVV / | MSV | MVV | FSV | MVV | MSV | MVV | MSV | FVV | | | |
| | 9 / 8 | 3.5 | 3.4 | 2.9 | 3.4 | 4.4 | 4.2 | 4.2 | 3.8 | 3.5 | 3.9 | 3.6 | 4.1 | 3.9 | 4.0 | 3.8 | 3.9 | 3.4 | | | |
| | | 37 | 37 | 36 | 37 | 38 | 37 | 37 | 38 | 37 | 39 | 38 | 38 | 38 | 37 | 37 | 39 | 37 | | | |
| 375 | | FSV | MVV | FSV | MVV | MSV | MVV | FSV | FVV | MSV / | FVV | MSV | FVV | MSV | MVV | MSV | FVV | | | | |
| | 9 / 7 | 3.5 | 4.2 | 3.8 | 3.9 | 4.5 | 4.2 | 3.9 | 4.1 | 4.3 | 4.3 | 4.1 | 4.1 | 4.2 | 4.2 | 4.5 | 3.7 | | | | |
| | | 35 | 39 | 36 | 38 | 40 | 39 | 37 | 37 | 38 | 37 | 39 | 37 | 39 | 39 | 35 | 37 | | | | |
| 376 | | FVV | MSV | FVV / | FSV | FVV | MSV | FVV | MSV | FVV | MSV | FVV | MSV | MVV | | | | | | | |
| | 4 / 11 | 3.8 | 4.2 | 3.7 | 3.3 | 3.5 | 3.8 | 3.9 | 4.1 | 3.5 | 3.8 | 3.7 | 3.8 | 2.8 | | | | | | | |
| | | 34 | 37 | 32 | 32 | 33 | 34 | 35 | 33 | 34 | 35 | 33 | 35 | 29 | | | | | | | |
| 377 | | FSV | FVV | MSV | FVV | MSV | E | / MVV | FSV | E | MVV | MSV | FVV | E | FSV | FVV | FSV | | | | |
| | 7 / 10 | 3.2 | 3.7 | 4.0 | 3.7 | 4.1 | NA | 3.7 | 3.5 | NA | 3.8 | 3.7 | 3.2 | NA | 3.5 | 3.5 | 3.3 | | | | |
| | | 34 | 33 | 36 | 35 | 36 | NA | 33 | 34 | NA | 34 | 32 | 31 | NA | 35 | 32 | 32 | | | | |
| 378 | | MVV | MSV | MVV | MSV | FVV | MSV | MVV | FSV / | MVV | MSV | MVV | FSV | FVV | MSV | FVV | | | | | |
| | 8 / 7 | 3.8 | 3.9 | 4.1 | 4.0 | 3.4 | 3.7 | 3.6 | 3.5 | 3.8 | 3.5 | 3.8 | 3.9 | 3.4 | 3.5 | 3.3 | | | | | |
| | | 37 | 34 | 34 | 35 | 35 | 36 | 35 | 35 | 35 | 36 | 36 | 34 | 34 | 35 | 33 | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 379 | | MVV | MSV | MVV | MSV / | MVV | MSV | FVV | MSV | FVV | MSV | FVV | FSV | MVV | | | | | | | |
| | 4 / 9 | 4.2 | 3.8 | 3.8 | 4.2 | 3.7 | 3.7 | 3.4 | 3.4 | 3.7 | 3.6 | 3.8 | 3.6 | 3.6 | | | | | | | |
| | | 39 | 37 | 35 | 37 | 34 | 36 | 36 | 34 | 34 | 33 | 35 | 34 | 34 | | | | | | | |
| 380 | | MSV | FVV | E | MSV | FVV / | MSV | FVV | MSV | FVV | FSV | MVV | FSV | | | | | | | | |
| | 7 / 11 | 3.8 | 3.9 | NA | 3.9 | 4.1 | 3.8 | 3.6 | 4.1 | 3.9 | 4.0 | 3.9 | 3.5 | | | | | | | | |
| | | 36 | 37 | NA | 36 | 36 | 38 | 36 | 40 | 38 | 37 | 36 | 36 | | | | | | | | |
| 381 | | MSV | FVV | MSV | MVV | MSV | MVV / | MSV | FVV | FSV | FVV | MSV | FVV | MSV | MVV | FSV | | | | | |
| | 6 / 9 | 3.6 | 3.5 | 3.6 | 3.9 | 3.5 | 3.3 | 3.8 | 3.5 | 3.7 | 3.7 | 3.9 | 3.3 | 3.7 | 3.7 | 3.4 | | | | | |
| | | 37 | 35 | 37 | 38 | 35 | 35 | 36 | 37 | 36 | 36 | 38 | 34 | 36 | 37 | 37 | | | | | |
| 382 | | FVV | FSV | FVV | FSV | FVV / | FSV | FVV | FSV | FVV | FSV | FVV | MSV | FVV | FSV | | | | | | |
| | 5 / 9 | 3.5 | 3.7 | 4.0 | 3.9 | 3.5 | 3.5 | 3.2 | 2.7 | 4.0 | 4.0 | 3.9 | 3.7 | 3.6 | 3.7 | | | | | | |
| | | 34 | 38 | 37 | 38 | 35 | 35 | 36 | 32 | 38 | 37 | 38 | 36 | 34 | 36 | | | | | | |
| 383 | | FVV | MSV | MVV | E | MSV | FVV | FSV | E | MVV | MSV | MVV | FSV | FVV / | FSV | MVV | MSV | FVV | MSV | FVV | |
| | 13 / 6 | 3.3 | 3.5 | 3.7 | NA | 3.6 | 3.5 | 3.9 | NA | 3.2 | 3.6 | 3.6 | 2.7 | 3.4 | 3.6 | 3.9 | 3.9 | 3.2 | 3.6 | 3.7 | |
| | | 35 | 36 | 36 | NA | 37 | 37 | 37 | NA | 35 | 34 | 35 | 34 | 34 | 36 | 39 | 38 | 37 | 37 | 37 | |
| 384 | | FVV | FSV | FVV | MSV | FVV | FSV | MVV | MSV | FVV | FSV / | MVV | FSV | MVV | | | | | | | |
| | 14 / 5 | 4.0 | 4.2 | 4.1 | 4.5 | 4.1 | 4.0 | 4.5 | 4.3 | 4.0 | 4.0 | 4.5 | 4.3 | 4.5 | | | | | | | |
| | | 36 | 39 | 38 | 39 | 36 | 37 | 40 | 39 | 37 | 37 | 39 | 38 | 38 | | | | | | | |
| 385 | | FSV | FVV | FSV | MVV | MSV | MVV | MSV / | MVV | MSV | MVV | FSV | FVV | MSV | MVV | MSV | | | | | |
| | 7 / 8 | 3.8 | 3.9 | 4.1 | 4.0 | 4.5 | 4.4 | 4.5 | 4.1 | 4.2 | 4.0 | 4.0 | 4.4 | 4.5 | 3.9 | 4.0 | | | | | |
| | | 37 | 37 | 36 | 39 | 39 | 41 | 39 | 39 | 38 | 37 | 38 | 38 | 38 | 35 | 36 | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 386 | | FVV | FSV | FVV | MSV | MVV | FSV | MVV / | MSV | FVV | MSV | MVV | MSV | MVV | FSV | MVV | MSV | MVV | FSV | MVV | FSV |
| | 8 / 17 | 3.7 | 3.7 | 3.6 | 4.0 | 3.9 | 3.6 | 3.7 | 3.8 | 3.9 | 3.7 | 3.5 | 3.8 | 4.0 | 3.8 | 3.8 | 3.6 | 3.8 | 3.5 | 3.7 | 3.5 |
| | | 38 | 39 | 38 | 35 | 37 | 36 | 37 | 35 | 36 | 37 | 36 | 38 | 37 | 36 | 37 | 36 | 37 | 36 | 36 | 34 |
| 387 | | MSV | FVV | FSV | FVV / | FSV | FVV | MSV | MVV | FSV | FVV | FSV | MVV | MSV | FVV | | | | | | |
| | 4 / 10 | 4.3 | 3.7 | 3.7 | 3.3 | 3.8 | 3.7 | 4.2 | 4.4 | 3.8 | 3.6 | 3.4 | 3.7 | 3.8 | 3.7 | | | | | | |
| | | 40 | 39 | 38 | 36 | 38 | 38 | 40 | 41 | 40 | 37 | 36 | 38 | 39 | 34 | | | | | | |
| 388 | | FVV | FSV | FVV | FSV | FVV | FSV | FVV | FSV | MVV / | MSV | MVV | FSV | FVV | | | | | | | |
| | 9 / 4 | 4.1 | 4.6 | 3.5 | 4.6 | 4.0 | 4.6 | 4.5 | 4.7 | 4.6 | 4.4 | 4.4 | 4.4 | 4.1 | | | | | | | |
| | | 40 | 38 | 38 | 10 | 38 | 39 | 41 | 39 | 42 | 40 | 39 | 40 | 38 | | | | | | | |
| 389 | | FSV | FVV | MSV | FVV | FSV | MVV | E | FSV | FVV | MSV / | E | MVV | E | FSV | FVV | | | | | |
| | 11 / 5 | 3.7 | 3.6 | 2.7 | 3.8 | 3.6 | 4.0 | NA | 3.7 | 3.6 | 3.8 | NA | 3.7 | NA | 3.5 | 3.2 | | | | | |
| | | 37 | 35 | 36 | 37 | 36 | 38 | NA | 37 | 36 | 37 | NA | 35 | NA | 35 | 36 | | | | | |
| 390 | | FVV | FSV | FVV | MSV | FVV | FSV / | MVV | MSV | FVV | FSV | MVV | FSV | MVV | MSV | FVV | | | | | |
| | 9 / 11 | 3.6 | 3.6 | 3.6 | 4.0 | 3.5 | 3.0 | 3.4 | 3.3 | 3.7 | 3.3 | 3.6 | 3.5 | 4.0 | 3.7 | 3.3 | | | | | |
| | | 35 | 37 | 35 | 35 | 35 | 35 | 34 | 34 | 37 | 32 | 36 | 36 | 33 | 36 | 36 | | | | | |
| 391 | | FSV | FVV | FSV | MVV / | FSV | FVV | MSV | E | FVV | E | MSV | MVV | E | | | | | | | |
| | 4 / 9 | 3.7 | 4.1 | 4.4 | 4.3 | 3.8 | 3.7 | 4.3 | NA | 4.0 | NA | 4.0 | 3.8 | NA | | | | | | | |
| | | 35 | 37 | 39 | 36 | 32 | 36 | 38 | NA | 35 | NA | 35 | 35 | NA | | | | | | | |
| 392 | | MVV | FSV | FVV | MSV | FVV | E | E | FSV / | MVV | MSV | FVV | MSV | MVV | FSV | FVV | MSV | | | | |
| | 10 / 12 | 3.2 | 3.5 | 3.7 | 3.4 | 3.8 | NA | NA | 3.6 | 3.5 | 3.7 | 3.3 | 3.8 | 3.6 | 3.2 | 3.0 | 2.9 | | | | |
| | | 35 | 34 | 34 | 36 | 38 | NA | NA | 35 | 36 | 36 | 36 | 36 | 35 | 33 | 33 | 32 | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 393 | | FVV | FSV | MVV | FSV | FVV / | MSV | MVV | MSV | FVV | MSV | FVV | | | | | | | | | |
| | 5 / 6 | 4.1 | 4.3 | 4.7 | 4.9 | 4.8 | 4.6 | 4.9 | 4.7 | 4.6 | 4.7 | 3.9 | | | | | | | | | |
| | | 35 | 37 | 36 | 37 | 36 | 36 | 36 | 36 | 37 | 36 | 35 | | | | | | | | | |
| 394 | | MSV | FVV | FSV | FVV | FSV | FVV | E | MSV | MVV | FSV / | | | | | | | | | | |
| | 11 / 7 | 3.8 | 3.6 | 3.6 | 3.9 | 3.8 | 3.8 | NA | 3.9 | 4.1 | 4.0 | | | | | | | | | | |
| | | 34 | 34 | 32 | 33 | 34 | 34 | NA | 35 | 35 | 35 | | | | | | | | | | |
| 395 | | FVV | MSV | FVV | L | FSV | FVV | FSV | FVV | FSV / | FVV | E | MSV | MVV | FSV | MVV | MSV | | | | |
| | 9 / 7 | 3.5 | 3.9 | 3.6 | NA | 3.6 | 3.5 | 3.5 | 3.5 | 3.5 | 3.7 | NA | 3.7 | 4 | 3.5 | 3.4 | 3.5 | | | | |
| | | 33 | 34 | 32 | NA | 31 | 31 | 34 | 33 | 35 | 34 | NA | 35 | 35 | 32 | 33 | 35 | | | | |
| 396 | | MSV | FVV | FSV | MVV | MSV | MVV | MSV | FVV | MSV / | MVV | MSV | MVV | FSV | MVV | E | FSV | MVV | FSV | FVV | |
| | 10 / 10 | 3.1 | 3.4 | 3.6 | 3.7 | 3.8 | 3.6 | 3.5 | 3.7 | 3.4 | 3.6 | 3.7 | 3.7 | 3.5 | 3.9 | NA | 3.5 | 3.7 | 3.2 | 3.3 | |
| | | 34 | 33 | 34 | 34 | 35 | 36 | 36 | 35 | 34 | 35 | 35 | 35 | 35 | 35 | NA | 36 | 36 | 35 | 34 | |
| 397 | NP | | | | | | | | | | | | | | | | | | | | |
| 398 | | MVV | MSV | MVV | MSV / | MVV | FSV | MVV | E | E | E | FSV | MVV | E | | | | | | | |
| | 5 / 11 | 3.6 | 3.4 | 4.0 | 3.6 | 3.2 | 3.7 | 4.2 | NA | NA | NA | 3.7 | 3.5 | NA | | | | | | | |
| | | 33 | 35 | 34 | 35 | 31 | 35 | 36 | NA | NA | NA | 34 | 33 | NA | | | | | | | |
| 399 | | FVV | MSV | FVV | MSV | MVV | MSV | FVV | FSV | MVV / | MSV | MVV | MSV | MVV | FSV | MVV | FSV | FVV | | | |
| | 9 / 8 | 3.5 | 3.8 | 3.5 | 3.9 | 3.8 | 3.6 | 2.9 | 3.5 | 3.8 | 3.7 | 3.5 | 3.8 | 3.5 | 3.6 | 3.5 | 3.4 | 3.3 | | | |
| | | 36 | 38 | 37 | 37 | 35 | 34 | 32 | 34 | 37 | 34 | 37 | 38 | 34 | 38 | 36 | 35 | 36 | | | |
| 400 | | E | FSV | MVV | MSV | MVV | FSV / | FVV | FSV | FVV | MSV | E | MVV | FSV | | | | | | | |
| | 6 / 7 | NA | 2.5 | 3.0 | 3.1 | 3.0 | 3.5 | 2.9 | 2.6 | 2.9 | 3.0 | NA | 3.0 | 3.2 | | | | | | | |
| | | NA | 30 | 33 | 34 | 33 | 36 | 35 | 32 | 32 | 33 | NA | 32 | 34 | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption L - Late Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right) NP - Not Pregnant
NA - Not Applicable/Not Available

MPI Research Study Number 952-002
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**Individual Animal Cesarean Section Data**
**Individual Fetal Body Weight Values, g**
**Individual Fetal Crown Rump Distance Values, mm**

| Group, Animal Number | CL | Implantation # 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | | | | | | | | | | | | | | | | | |
| 401 | | MVV | MSV | FVV | MSV | FVV / | MSV | MVV | MSV | MVV | FSV | FVV | FSV | MVV | MSV | MVV | FSV | | | | |
| | 5 / 11 | 4.0 | 4.1 | 3.9 | 4.2 | 1.6 | 3.8 | 3.9 | 3.8 | 3.9 | 3.9 | 4.1 | 4.0 | 4.1 | 4.0 | 3.8 | 3.4 | | | | |
| | | 34 | 35 | 37 | 37 | 24 | 35 | 37 | 34 | 33 | 34 | 35 | 39 | 36 | 35 | 38 | 35 | | | | |
| 402 | | FSV | MVV | MSV | FVV | MSV | E | / FVV | MSV | FVV | FSV | FVV | FSV | MVV | | | | | | | |
| | 6 / 7 | 3.5 | 3.7 | 3.9 | 3.7 | 3.9 | NA | 3.6 | 4.0 | 3.8 | 3.8 | 3.8 | 3.4 | 3.8 | | | | | | | |
| | | 33 | 35 | 34 | 33 | 36 | NA | 33 | 35 | 35 | 34 | 35 | 31 | 33 | | | | | | | |
| 403 | | MVV | FSV | MVV | MSV | E | MVV | MSV / | FVV | FSV | FVV | FSV | MVV | MSV | MVV | E | | | | | |
| | 7 / 8 | 3.6 | 3.1 | 3.9 | 3.1 | NA | 3.9 | 3.9 | 3.1 | 3.2 | 3.7 | 3.9 | 3.4 | 3.7 | 3.9 | NA | | | | | |
| | | 32 | 32 | 35 | 32 | NA | 34 | 34 | 33 | 32 | 33 | 34 | 33 | 35 | 34 | NA | | | | | |
| 404 | | FSV | FVV | MSV | MVV | MSV | FVV / | FSV | MVV | MSV | FVV | E | MSV | | | | | | | | |
| | 7 / 7 | 3.7 | 3.6 | 4.1 | 4.2 | 4.3 | 3.8 | 3.7 | 4.0 | 4.4 | 4.1 | NA | 3.8 | | | | | | | | |
| | | 36 | 33 | 34 | 37 | 37 | 34 | 35 | 36 | 36 | 35 | NA | 35 | | | | | | | | |

SEX CODES: M - Male F - Female
EXAMINATION CODES: S - Skeletal V - Visceral
FETAL STATUS CODES: V - Viable Fetus E - Early Resorption
CL - Corpora Lutea / - Denotes position of cervix (Left/Right)
NA - Not Applicable/Not Available

# APPENDIX L
Individual Gravid Uterine Weight and
Adjusted Body Weight/Body Weight Change Values

**Individual Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values, g**

| Group, Animal Number | Gravid Uterine Weight | Final Body Weight | Adjusted Final Body Weight | Weight Change from Day 0 | Adjusted Weight Change from Day 0 |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 301 | 74 | 349 | 275 | 110 | 36 |
| 302 | 76 | 337 | 261 | 118 | 42 |
| 303 | 66 | 337 | 271 | 127 | 61 |
| 304 | 78 | 371 | 293 | 142 | 64 |
| 305 | 85 | 377 | 292 | 144 | 59 |
| 306 | 18 | 268 | 250 | 75 | 57 |
| 307 | 82 | 350 | 268 | 129 | 47 |
| 308 | 84 | 359 | 275 | 115 | 31 |
| 309 | 57 | 335 | 278 | 117 | 60 |
| 310 | 84 | 380 | 296 | 149 | 65 |
| 311 | 81 | 370 | 289 | 124 | 43 |
| 312 | 84 | 360 | 276 | 127 | 43 |
| 313 | 72 | 369 | 297 | 133 | 61 |
| 315 | 81 | 351 | 270 | 131 | 50 |
| 316 | 57 | 332 | 275 | 96 | 39 |
| 317 | 85 | 355 | 270 | 120 | 35 |
| 318 | 64 | 385 | 321 | 132 | 68 |
| 319 | 96 | 383 | 287 | 145 | 49 |
| 320 | 70 | 351 | 281 | 108 | 38 |
| 321 | 69 | 335 | 266 | 91 | 22 |
| 322 | 76 | 367 | 291 | 133 | 57 |
| 323 | 98 | 393 | 295 | 154 | 56 |
| 324 | 82 | 376 | 294 | 127 | 45 |
| 325 | 88 | 399 | 311 | 139 | 51 |
| 326 | 86 | 370 | 284 | 131 | 45 |

**Individual Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values, g**

| Group, Animal Number | Gravid Uterine Weight | Final Body Weight | Adjusted Final Body Weight | Weight Change from Day 0 | Adjusted Weight Change from Day 0 |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 327 | 62 | 305 | 243 | 106 | 44 |
| 328 | 90 | 382 | 292 | 142 | 52 |
| 329 | 79 | 367 | 288 | 139 | 60 |
| 330 | 80 | 391 | 311 | 157 | 77 |
| 331 | 68 | 319 | 251 | 108 | 40 |
| 332 | 85 | 384 | 299 | 141 | 56 |
| 333 | 58 | 313 | 255 | 99 | 41 |
| 334 | 79 | 342 | 263 | 130 | 51 |
| 335 | 87 | 391 | 304 | 148 | 61 |
| 336 | 69 | 361 | 292 | 145 | 76 |
| 337 | 55 | 347 | 292 | 100 | 45 |
| 338 | 15 | 298 | 283 | 60 | 45 |
| 339 | 76 | 339 | 263 | 122 | 46 |
| 341 | 58 | 323 | 265 | 104 | 46 |
| 342 | 72 | 360 | 288 | 109 | 37 |
| 343 | 80 | 344 | 264 | 127 | 47 |
| 344 | 79 | 320 | 241 | 111 | 32 |
| 345 | 52 | 328 | 276 | 99 | 47 |
| 346 | 81 | 377 | 296 | 132 | 51 |
| 347 | 73 | 344 | 271 | 116 | 43 |
| 348 | 82 | 373 | 291 | 143 | 61 |
| 349 | 77 | 353 | 276 | 109 | 32 |
| 350 | 77 | 366 | 289 | 132 | 55 |
| 351 | 93 | 395 | 302 | 147 | 54 |
| 352 | 89 | 390 | 301 | 153 | 64 |

**Individual Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values, g**

| Group, Animal Number | Gravid Uterine Weight | Final Body Weight | Adjusted Final Body Weight | Weight Change from Day 0 | Adjusted Weight Change from Day 0 |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 353 | 68 | 332 | 264 | 120 | 52 |
| 354 | 77 | 370 | 293 | 142 | 65 |
| 355 | 74 | 386 | 312 | 147 | 73 |
| 356 | 74 | 356 | 282 | 148 | 74 |
| 357 | 92 | 397 | 305 | 163 | 71 |
| 358 | 66 | 332 | 266 | 114 | 48 |
| 359 | 77 | 361 | 284 | 127 | 50 |
| 360 | 80 | 376 | 296 | 132 | 52 |
| 361 | 84 | 383 | 299 | 159 | 75 |
| 362 | 82 | 383 | 301 | 131 | 49 |
| 363 | 90 | 373 | 283 | 158 | 68 |
| 364 | 81 | 364 | 283 | 124 | 43 |
| 365 | 81 | 369 | 288 | 150 | 69 |
| 366 | 72 | 361 | 289 | 116 | 44 |
| 367 | 91 | 349 | 258 | 134 | 43 |
| 368 | 72 | 382 | 310 | 127 | 55 |
| 369 | 66 | 355 | 289 | 125 | 59 |
| 370 | 90 | 363 | 273 | 129 | 39 |
| 371 | 45 | 355 | 310 | 111 | 66 |
| 372 | 82 | 367 | 285 | 148 | 66 |
| 373 | 68 | 350 | 282 | 103 | 35 |
| 374 | 94 | 406 | 312 | 168 | 74 |
| 375 | 93 | 397 | 304 | 127 | 34 |
| 376 | 79 | 378 | 299 | 128 | 49 |
| 377 | 74 | 374 | 300 | 125 | 51 |
| 378 | 83 | 383 | 300 | 126 | 43 |

**Individual Gravid Uterine Weight and Adjusted Body Weight/Body Weight Change Values, g**

| Group, Animal Number | Gravid Uterine Weight | Final Body Weight | Adjusted Final Body Weight | Weight Change from Day 0 | Adjusted Weight Change from Day 0 |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 379 | 70 | 325 | 255 | 121 | 51 |
| 380 | 63 | 358 | 295 | 119 | 56 |
| 381 | 80 | 360 | 280 | 156 | 76 |
| 382 | 77 | 350 | 273 | 123 | 46 |
| 383 | 89 | 398 | 309 | 153 | 64 |
| 384 | 78 | 367 | 289 | 139 | 61 |
| 385 | 88 | 391 | 303 | 132 | 44 |
| 386 | 106 | 423 | 317 | 174 | 68 |
| 387 | 77 | 344 | 267 | 125 | 48 |
| 388 | 83 | 377 | 294 | 138 | 55 |
| 389 | 67 | 355 | 288 | 130 | 63 |
| 390 | 79 | 372 | 293 | 124 | 45 |
| 391 | 63 | 333 | 270 | 107 | 44 |
| 392 | 76 | 385 | 309 | 127 | 51 |
| 393 | 74 | 361 | 287 | 121 | 47 |
| 394 | 49 | 336 | 287 | 109 | 60 |
| 395 | 80 | 354 | 274 | 116 | 36 |
| 396 | 95 | 415 | 320 | 156 | 61 |
| 398 | 51 | 348 | 297 | 96 | 45 |
| 399 | 89 | 391 | 302 | 138 | 49 |
| 400 | 55 | 341 | 286 | 105 | 50 |
| 401 | 90 | 384 | 294 | 145 | 55 |
| 402 | 71 | 378 | 307 | 123 | 52 |
| 403 | 75 | 393 | 318 | 141 | 66 |
| 404 | 68 | 348 | 280 | 115 | 47 |

# APPENDIX M
Individual Fetal External, Visceral, and Skeletal Observations

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 301 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 302 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 302 Cont. | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 303 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 304 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 304 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 305 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 305 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 306 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| 307 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 308 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 308 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 309 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 310 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 311 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 311 Cont. | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 312 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 312 Cont. | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 313 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 315 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 315 Cont. | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 316 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 317 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 318 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 318 Cont. | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 319 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 320 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 321 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 321 Cont. | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 322 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 323 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 323 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 324 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 324 Cont. | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 325 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 326 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 327 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 328 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 328 Cont. | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 329 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 330 | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 330 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 331 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 331 Cont. | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 332 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 333 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 334 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 334 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 335 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 336 | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 337 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 338 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| 339 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 341 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 341 Cont. | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 342 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 343 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 343 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 344 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 344 Cont. | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 345 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| 346 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 346 Cont. | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 347 | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 348 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 348 Cont. | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 349 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 349 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 350 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 351 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 351 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 352 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 352 Cont. | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 353 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 354 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 354 Cont. | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 355 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 356 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 356 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 357 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 357 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 358 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 359 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 359 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 360 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 360 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 361 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 362 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 362 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 363 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 363 Cont. | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 364 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 365 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 365 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 366 | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 366 Cont. | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 367 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 368 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 369 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 369 Cont. | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| 370 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 371 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 371 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 372 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 373 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 373 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 374 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 374 Cont. | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 375 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 376 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 377 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

MPI Research Study Number 952-002
An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 377 Cont. | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 378 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 379 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 380 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 380 Cont. | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 381 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 382 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 382 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 383 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 383 Cont. | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |
| 384 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 385 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 385 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 386 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 386 Cont. | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |
| | 20 | | | | No abnormalities detected |
| 387 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 388 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 389 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 389 Cont. | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 390 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 391 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 391 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 392 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 393 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| 394 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 395 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 396 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 396 Cont. | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |
| 398 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 399 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 399 Cont. | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 400 | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 400 Cont. | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 401 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 402 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 402 Cont. | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 403 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal External Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 404 | 1 | | | | No abnormalities detected |
| | 2 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 301 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 302 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 303 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 304 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 305 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 306 | 1 | | | | No abnormalities detected |
| 307 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 308 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 309 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 310 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 311 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 312 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 313 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 313 Cont. | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 315 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 316 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 317 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 317 Cont. | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 318 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 319 | 1 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |
| 320 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 320 Cont. | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 321 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 322 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 323 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 324 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 325 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 325 Cont. | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 326 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 327 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| 328 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 329 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 330 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 331 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 332 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 333 | 1 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 334 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 335 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 336 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 337 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 338 | 1 | | | | No abnormalities detected |
| 339 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 341 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 342 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 343 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 344 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 345 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| 346 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 347 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 347 Cont. | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 348 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 349 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 350 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 351 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 352 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 353 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 354 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 355 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 356 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 357 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 358 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 359 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 360 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 361 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 362 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 363 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 364 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 365 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 366 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 367 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 368 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 369 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| 370 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 371 | 1 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| 372 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 373 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 374 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 374 Cont. | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 375 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 376 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 377 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 378 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 379 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 380 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| 381 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 382 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 383 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |
| 384 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 385 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 386 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |
| 387 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 387 Cont. | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 388 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 389 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 390 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 390 Cont. | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 391 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 392 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 393 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 394 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| 395 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 396 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| | 19 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 398 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 399 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | | | | No abnormalities detected |
| 400 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 401 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Head | Eye(s) | M | Anophthalmia |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 402 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 403 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

M- Malformation

**Individual Fetal Visceral Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 404 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 301 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Skull | Hyoid | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| 302 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | Rib(s) | Rib(s) | V | Rudimentary |
| | 14 | | | | No abnormalities detected |
| 303 | 1 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Misaligned |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 304 | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 14 | | | | No abnormalities detected |
| 305 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Rib(s) | Rib(s) | V | Rudimentary |
| | 11 | | | | No abnormalities detected |
| | 13 | Rib(s) | Rib(s) | V | Rudimentary |
| | 15 | Skull | Hyoid | V | Not ossified |
| 306 | 2 | | | | No abnormalities detected |
| 307 | 1 | | | | No abnormalities detected |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 307 Cont. | 9 | | | | No abnormalities detected |
| | 11 | Skull | Hyoid | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | | | | No abnormalities detected |
| 308 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 309 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | | | | No abnormalities detected |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | | | | No abnormalities detected |
| 310 | 2 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 310 Cont. | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Misaligned |
| 311 | 1 | Skull | Hyoid | V | Not ossified |
| | 1 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Skull | Hyoid | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Skull | Hyoid | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Skull | Hyoid | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Skull | Hyoid | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | Skull | Hyoid | V | Not ossified |
| | 16 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 312 | 2 | | | | No abnormalities detected |
| | 4 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | Forelimb(s) | Metacarpals | V | Not ossified |
| 313 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 315 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 315 Cont. | 9 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Rib(s) | Rib(s) | V | Rudimentary |
| | 13 | Rib(s) | Rib(s) | V | Unilateral full rib |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| 316 | 1 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Skull | Hyoid | V | Not ossified |
| | 7 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| 317 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Forelimb(s) | Metacarpals | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 317 Cont. | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 318 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 319 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| | 17 | Skull | Hyoid | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 320 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 321 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Skull | Hyoid | V | Not ossified |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 322 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 323 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 324 | 1 | Skull | Hyoid | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | | | | No abnormalities detected |
| | 9 | Sternum | Sternebra(e) | V | Misaligned |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | Skull | Hyoid | V | Not ossified |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 0 mg/M$^3$ | | | | | |
| 325 | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | | | | No abnormalities detected |
| 326 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 15 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 327 | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 328 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Rib(s) | Rib(s) | V | Rudimentary |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | Rib(s) | Rib(s) | V | Rudimentary |
| | 13 | | | | No abnormalities detected |
| | 15 | Rib(s) | Rib(s) | V | Rudimentary |
| 329 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 329 Cont. | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 15 | Skull | Hyoid | V | Not ossified |
| 330 | 2 | Skull | Interparietal bone | V | Incompletely ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Rib(s) | Rib(s) | V | Rudimentary |
| | 6 | Rib(s) | Rib(s) | V | Rudimentary |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Skull | Hyoid | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 15 | Skull | Hyoid | V | Not ossified |
| | 17 | | | | No abnormalities detected |
| 331 | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Rib(s) | Rib(s) | V | Rudimentary |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 331 Cont. | 10 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| 332 | 1 | | | | No abnormalities detected |
| | 3 | Skull | Hyoid | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Rib(s) | Rib(s) | V | Rudimentary |
| | 11 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 11 | Rib(s) | Rib(s) | V | Rudimentary |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 333 | 3 | Skull | Hyoid | V | Not ossified |
| | 6 | Rib(s) | Rib(s) | V | Rudimentary |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 8 | Rib(s) | Rib(s) | V | Rudimentary |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 334 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Skull | Frontal bone | V | Incompletely ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 15 | | | | No abnormalities detected |
| 335 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | | | | No abnormalities detected |
| | 15 | Forelimb(s) | Metacarpals | V | Not ossified |
| 336 | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 337 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| 338 | 2 | Skull | Hyoid | V | Not ossified |
| 339 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 13 | Forelimb(s) | Metacarpals | V | Not ossified |
| 341 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Rib(s) | Rib(s) | V | Rudimentary |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 342 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 6 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| 343 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 343 Cont. | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 344 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Rib(s) | Rib(s) | V | Rudimentary |
| | 6 | Rib(s) | Rib(s) | V | Unilateral full rib |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 345 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| 346 | 2 | Skull | Hyoid | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 8 | Skull | Hyoid | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 346 Cont. | 10 | Skull | Hyoid | V | Not ossified |
| | 12 | Skull | Hyoid | V | Not ossified |
| | 14 | Skull | Hyoid | V | Not ossified |
| 347 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | Skull | Hyoid | V | Not ossified |
| | 14 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| 348 | 2 | | | | No abnormalities detected |
| | 4 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | Skull | Hyoid | V | Not ossified |
| | 7 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | Skull | Hyoid | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 348 Cont. | 11 | Skull | Hyoid | V | Not ossified |
| | 11 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 15 | | | | No abnormalities detected |
| 349 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 350 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 12 | | | | No abnormalities detected |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 2.6 mg/M$^3$ | | | | | |
| 351 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | Rib(s) | Rib(s) | V | Rudimentary |
| | 13 | | | | No abnormalities detected |
| | 15 | Sternum | Sternebra(e) | V | Not ossified |
| | 17 | Sternum | Sternebra(e) | V | Not ossified |
| 352 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 353 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 354 | 2 | | | | No abnormalities detected |
| | 4 | Rib(s) | Rib(s) | V | Unilateral full rib |
| | 6 | | | | No abnormalities detected |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 355 | 1 | Skull | Hyoid | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 355 Cont. | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| 356 | 2 | Rib(s) | Rib(s) | V | Rudimentary |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | Rib(s) | Rib(s) | V | Rudimentary |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| 357 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | | | | No abnormalities detected |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 358 | 2 | | | | No abnormalities detected |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | | | | No abnormalities detected |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 359 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | Sternum | Sternebra(e) | V | Not ossified |
| 360 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 360 Cont. | 14 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 361 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | Rib(s) | Rib(s) | V | Rudimentary |
| 362 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 363 | 2 | | | | No abnormalities detected |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 6 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 363 Cont. | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 364 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 365 | 2 | Skull | Hyoid | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 366 | 2 | Rib(s) | Rib(s) | V | Rudimentary |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| 367 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Rib(s) | Rib(s) | V | Rudimentary |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Rib(s) | Rib(s) | V | Rudimentary |
| | 16 | Rib(s) | Rib(s) | V | Rudimentary |
| 368 | 1 | Skull | Hyoid | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 368 Cont. | 7 | Sternum | Sternebra(e) | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | | | | No abnormalities detected |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| 369 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 370 | 1 | | | | No abnormalities detected |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | | | | No abnormalities detected |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | | | | No abnormalities detected |
| | 14 | Rib(s) | Rib(s) | V | Rudimentary |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 371 | 3 | | | | No abnormalities detected |
| | 5 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 372 | 1 | | | | No abnormalities detected |
| | 3 | Skull | Hyoid | V | Not ossified |
| | 5 | Skull | Hyoid | V | Not ossified |
| | 7 | Skull | Hyoid | V | Not ossified |
| | 7 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 373 | 1 | | | | No abnormalities detected |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 374 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 8 | Rib(s) | Rib(s) | V | Unilateral full rib |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 375 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 376 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 4.4 mg/M$^3$ | | | | | |
| 376 Cont. | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| 377 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 378 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 379 | 2 | Skull | Hyoid | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | Skull | Hyoid | V | Not ossified |
| 380 | 1 | Skull | Hyoid | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| 381 | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Skull | Hyoid | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 381 Cont. | 13 | Skull | Hyoid | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| | 15 | Skull | Hyoid | V | Not ossified |
| | 15 | Sternum | Sternebra(e) | V | Not ossified |
| 382 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | Skull | Hyoid | V | Not ossified |
| | 14 | Skull | Hyoid | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| 383 | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 384 | 2 | Skull | Hyoid | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 4 | Skull | Interparietal bone | V | Incompletely ossified |
| | 6 | Skull | Hyoid | V | Not ossified |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 12 | Skull | Hyoid | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| 385 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| | 15 | | | | No abnormalities detected |
| 386 | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 386 Cont. | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| | 18 | | | | No abnormalities detected |
| | 20 | | | | No abnormalities detected |
| 387 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |
| | 13 | | | | No abnormalities detected |
| 388 | 2 | | | | No abnormalities detected |
| | 4 | Rib(s) | Rib(s) | V | Rudimentary |
| | 6 | | | | No abnormalities detected |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 389 | 1 | | | | No abnormalities detected |
| | 3 | Skull | Hyoid | V | Not ossified |
| | 3 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 3 | Sternum | Sternebra(e) | V | Not ossified |
| | 5 | | | | No abnormalities detected |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| 390 | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | | | | No abnormalities detected |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 14 | | | | No abnormalities detected |
| 391 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 11 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 392 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 393 | 2 | | | | No abnormalities detected |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 6 | | | | No abnormalities detected |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 10 | Skull | Hyoid | V | Not ossified |
| 394 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| 395 | 2 | Rib(s) | Rib(s) | V | Rudimentary |
| | 5 | Rib(s) | Rib(s) | V | Rudimentary |
| | 7 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 395 Cont. | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | Rib(s) | Rib(s) | V | Rudimentary |
| | 16 | | | | No abnormalities detected |
| 396 | 1 | | | | No abnormalities detected |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | Skull | Hyoid | V | Not ossified |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Skull | Hyoid | V | Not ossified |
| | 13 | | | | No abnormalities detected |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| | 18 | Sternum | Sternebra(e) | V | Not ossified |
| 398 | 2 | | | | No abnormalities detected |
| | 4 | | | | No abnormalities detected |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | | | | No abnormalities detected |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 399 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 6 | | | | No abnormalities detected |
| | 8 | Skull | Hyoid | V | Not ossified |
| | 8 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |
| | 10 | Skull | Hyoid | V | Not ossified |
| | 10 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 12 | Skull | Hyoid | V | Not ossified |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |
| | 14 | Skull | Hyoid | V | Not ossified |
| | 14 | Sternum | Sternebra(e) | V | Not ossified |
| | 16 | Skull | Hyoid | V | Not ossified |
| | 16 | Sternum | Sternebra(e) | V | Not ossified |
| 400 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | | | | No abnormalities detected |
| | 6 | | | | No abnormalities detected |
| | 8 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 400 Cont. | 10 | Skull | Hyoid | V | Not ossified |
| | 10 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 10 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Skull | Hyoid | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| 401 | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 2 | Rib(s) | Rib(s) | V | Rudimentary |
| | 2 | Rib(s) | Rib(s) | V | Unilateral full rib |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 4 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 6 | Sternum | Sternebra(e) | V | Not ossified |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |
| | 14 | | | | No abnormalities detected |
| | 16 | | | | No abnormalities detected |
| 402 | 1 | | | | No abnormalities detected |
| | 3 | Rib(s) | Rib(s) | V | Rudimentary |
| | 5 | | | | No abnormalities detected |
| | 8 | | | | No abnormalities detected |
| | 10 | | | | No abnormalities detected |
| | 12 | Sternum | Sternebra(e) | V | Not ossified |

V- Variation

**Individual Fetal Skeletal Observations**

| Group, Animal Number | Fetus Number | Area | Location | Classification | Observation |
|---|---|---|---|---|---|
| 6.3 mg/M$^3$ | | | | | |
| 403 | 2 | Skull | Hyoid | V | Not ossified |
| | 2 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 2 | Sternum | Sternebra(e) | V | Not ossified |
| | 4 | Skull | Hyoid | V | Not ossified |
| | 4 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 4 | Sternum | Sternebra(e) | V | Not ossified |
| | 7 | | | | No abnormalities detected |
| | 9 | Sternum | Sternebra(e) | V | Not ossified |
| | 11 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 11 | Sternum | Sternebra(e) | V | Not ossified |
| | 13 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 13 | Sternum | Sternebra(e) | V | Not ossified |
| 404 | 1 | Forelimb(s) | Metacarpals | V | Not ossified |
| | 1 | Sternum | Sternebra(e) | V | Not ossified |
| | 3 | | | | No abnormalities detected |
| | 5 | | | | No abnormalities detected |
| | 7 | | | | No abnormalities detected |
| | 9 | | | | No abnormalities detected |
| | 12 | | | | No abnormalities detected |

V- Variation

# APPENDIX N
Historical Control Data

## Historical Control Data – MPI Research
## Developmental Toxicity Data
## Crl: CD (SD) BR Rats
## 1995-2000

| | Mated In-house (1995-1997) | | Time-mated by Supplier[1] (1997-2000) | |
|---|---|---|---|---|
| Number of Studies[2] | 5 | | 9 | |
| Number of Animals | 150 | | 242 | |
| No. Pregnant | 129 | | 232 | |
| No. Died | 0 | | 1 | |
| No. of Resorptions Only | 1 | | 0 | |
| No. With Fetuses | 128 | | 231 | |
| **Parameter** | **Mean** | **Range of Study Values** | **Mean** | **Range of Study Values** |
| Pregnancy Rate (%) | 86.0 | 80 – 97 | 96 | 85 – 100 |
| No. Corpora Lutea | 18.0 | 17 – 19 | 15 | 13 – 16 |
| Preimplantation Loss (%) | 9.8 | 7 – 11 | 13 | 7 – 18 |
| No. Live Fetuses | 15.0 | 14 – 16 | 12 | 11 – 13 |
| No. Early Resorption Sites | 1 | 1 – 1 | 1 | 0 – 1 |
| No. Late Resorption Sites | 0 | 0 | 0 | 0 |
| No. Total Resorption Sites | 1 | 1 – 1 | 1 | 0-1 |
| Postimplantation Loss (%) | 8.2 | 7 – 9 | 6 | 4 – 8 |
| Fetal Sex Ratio (% Males) | 49.6 | 47 – 51 | 50 | 46 – 55 |
| Fetal Body Weight (g) - Combined | 4 | 4 – 4 | 4 | 4 – 4 |
| Fetal Body Weight (g) - Male | 4 | 4 – 4 | 4 | 4 – 4 |
| Fetal Body Weight (g) - Female | 4 | 4 – 4 | 4 | 4 – 4 |

[1] Portage, Michigan Facility of Charles River Laboratories
[2] Definitive developmental toxicity studies exclusive of range-finding studies.

## Historical Control Data – MPI Research
## Developmental Toxicity Data
## Crl: CD (SD) BR Rats
## 1995-2000

| | Mated In-house (1995-1997) | | Time-mated by Supplier[1] (1997-2000) | |
|---|---|---|---|---|
| No. of Studies[2] | 5 | | 9 | |
| No. Fetuses Evaluated - External | 1900 | | 2800 | |
| No. Fetuses Evaluated - Visceral | 947 | | 1401 | |
| No. Fetuses Evaluated - Skeletal | 953 | | 1400 | |
| Total No. Litters Evaluated | 128 | | 231 | |
| **Malformations:** | **Total No. Fetuses (Litters) Affected** | **Max % / study- Fetuses (Litters) Affected** | **Total No. Fetuses (Litters) Affected** | **Max % / study- Fetuses (Litters) Affected** |
| Abdominal Cavity, Situs Inversus | | | 1 (1) | 0.7 (4.5) |
| Abdominal Cavity, Diaphragm, Hernia | | | 1 (1) | 0.6 (3.4) |
| Appendicular, Femur, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Appendicular, Fibula, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Appendicular, Humerus, Bent | | | 1 (1) | 0.7 (4.2) |
| Appendicular, Humerus, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Appendicular, Radius, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Appendicular, Tibia, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Appendicular, Ulna, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Cephalic, Brain, Internal Hydrocephaly | | | 1 (1) | 0.7 (4.2) |
| Cephalic, Encephalocele | | | 1 (1) | 0.3 (4.0) |
| Cephalic, Exencephaly | | | 3 (1) | 0.8 (3.4) |
| Cephalic, Eyelid, Absent | | | 2 (1) | 0.6 (3.4) |
| Cephalic, Eyes, Malpositioned | 1 (1) | 0.5 (3.4) | | |
| Cephalic, Eyes. Microphthalmia | 1 (1) | 0.2 (3.4) | 2 (2) | 0.6 (4.0) |
| Cephalic, Head, Cleft Face | | | 1(1) | 0.3 (3.4) |
| Cephalic, Incisor, Absent | | | 1 (1) | 0.6 (4.0) |
| Cephalic, Jaw, Short | | | 1 (1) | 0.6 (4.0) |
| Cephalic, Lip, Cleft | | | 1 (1) | 0.3 (3.4) |
| Cephalic, Palate, Cleft | | | 4 (2) | 0.8 (4.3) |
| Cephalic, Retina, Folded | 3 (3) | 1.6 (13.0) | 6 (5) | 1.5 (6.7) |
| Body, Edema | | | 1 (1) | 0.3 (4.0) |
| Body, Entire Body Short | 1 (1) | 0.5 (4.0) | | |
| Pectoral Girdle, Scapula, Bent | | | 1 (1) | 0.7 (4.2) |
| Pelvic, Ilium, Malpositioned, | 1 (1) | 0.5 (4.0) | | |
| Pelvic, Ilium, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Pelvic, Ischium, Malpositioned | 1 (1) | 0.5 (4.0) | | |
| Pelvic, Ischium, Smaller than Normal | | | 1 (1) | 0.6 (4.0) |
| Pelvic, Tail, Filamentus | 1 (1) | 0.3 (4.0) | | |
| Renal, Anal, Absent | 1 (1) | 0.3 (4.0) | | |
| Ribs, Absent | 1 (1) | 0.5 (4.0) | | |
| Skull, C1 Arch, Malpositioned | | | 1 (1) | 0.5 (3.4) |
| Skull, Exoccipital Bone, Malpositioned | | | 1 (1) | 0.5 (3.4) |
| Skull, Frontals, Smaller than Normal | | | 3 (1) | 1.7 (3.4) |

[1] Portage, Michigan Facility of Charles River Laboratories
[2] Definitive developmental toxicity studies exclusive of range-finding studies.

## Historical Control Data – MPI Research
## Developmental Toxicity Data
## Crl: CD (SD) BR Rats
## 1995-2000

| | Mated In-house (1995-1997) | | Time-mated by Supplier[1] (1997-2000) | |
|---|---|---|---|---|
| **Malformations:** | **Total No. Fetuses (Litters) Affected** | **Max % / study- Fetuses (Litters) Affected** | **Total No. Fetuses (Litters) Affected** | **Max % / study- Fetuses (Litters) Affected** |
| Skull, Interparietals, Absent | | | 3 (1) | 1.7 (3.4) |
| Skull, Nasals, Smaller than Normal | | | 3 (1) | 1.7 (3.4) |
| Skull, Parietals, Smaller than Normal | | | 3 (1) | 1.7 (3.4) |
| Skull, Premaxilla, Smaller than Normal | | | 3 (1) | 1.7 (3.4) |
| Skull, Malpositioned | | | 3 (1) | 1.7 (3.4) |
| Skull, Squamosal, Smaller than Normal | | | 3 (1) | 1.7 (3.4) |
| Skull, Supraoccipital, Absent | | | 1 (1) | 0.6 (3.4) |
| Skull, Supraoccipital, Smaller than Normal | | | 2 (1) | 1.1 (3.4) |
| Skull, Upper Incisor, Absent | | | 1 (1) | 0.6 (3.4) |
| Sternum, Sternebra, Fused | | | 1 (1) | 0.6 (4.0) |
| Thoracic Cavity, Situs Inversus | | | 1 (1) | 0.7 (4.5) |
| Vertebral Column, Caudal Neural Arches, Absent | 1 (1) | 0.5 (4.0) | | |
| Vertebral Column, Lumbar Neural Arches, Absent | 1 (1) | 0.5 (4.0) | | |
| Vertebral Column, Sacral Neural Arches, Absent | 1 (1) | 0.5 (4.0) | | |
| Vertebral Column, Thoracic Neural Arches, Absent | 1 (1) | 0.5 (4.0) | | |
| Vertebral Column, Thoracic Neural Arches, Fused | 1 (1) | 0.5 (4.0) | | |
| Vertebral Column, Thoracic Neural Arches, Malpositioned | 1 (1) | 0.5 (4.0) | | |

[1] Portage, Michigan Facility of Charles River Laboratories

## Historical Control Data – MPI Research
## Developmental Toxicity Data
## Crl: CD (SD) BR Rats
## 1995-2000

| | Mated In-house (1995-1997) | | Time-mated by Supplier[1] (1997-2000) | |
|---|---|---|---|---|
| No. of Studies[2] | 5 | | 9 | |
| No. Fetuses Evaluated - External | 1900 | | 2800 | |
| No. Fetuses Evaluated - Visceral | 947 | | 1401 | |
| No. Fetuses Evaluated - Skeletal | 953 | | 1400 | |
| Total No. Litters Evaluated | 128 | | 231 | |
| **Variations:** | **Total No. Fetuses (Litters ) Affected** | **Max % / study- Fetuses (Litters) Affected** | **Total No. Fetuses (Litters) Affected** | **Max % / study- Fetuses (Litters) Affected** |
| Abdominal Cavity, Ureter, Dilated | | | 1 (1) | 0.6 (3.4) |
| Cervical Vertebra, Neural Arch, Additional Ossification Center | | | 3 (3) | 1.2 (6.9) |
| Pelvic, Ischium, Incomplete Ossification | 7 (6) | 1.6 (8.7) | 3 (3) | 0.7 (4.3) |
| Pelvic, Pubis, Not Ossified | | | 2 (2) | 0.7 (4.0) |
| Pelvic, Tail, Bent | 1 (1) | 0.3 (4.3) | 1 (1) | 0.3 (4.0) |
| Renal, Kidney, Increased Renal Pelvic Cavitation | 3 (3) | 0.5 (4.3) | 4 (4) | 1.1 (6.9) |
| Renal, Ureter, Dilated | 22 (18) | 3.3 (26.1) | 24 (15) | 9.3 (28.0) |
| Ribs, Cervical Neural Arches, Additional Ossification Center | 2 (2) | 0.5 (3.8) | 6 (4) | 2.6 (7.7) |
| Ribs, Additional Ossification Center | 1 (1) | 0.5 (4.0) | 4 (4) | 1.4 (8.3) |
| Rib, Bent | 2 (2) | 0.6 (4.3) | 7 (7) | 1.4 (8.3) |
| Rib, Rudimentary | 212 (80) | 25.7 (72.4) | 263 (124) | 25.8 (72.0) |
| Rib, Unilateral Full Rib | 4 (4) | 1.1 (8.0) | 1 (1) | 0.6 (4.0) |
| Skull, Hyoid, Not Ossified | 35 (22) | 6.9 (24.0) | 23 (13) | 12.1 (39.1) |
| Skull, Interparietals, Incomplete Ossification | 1 (1) | 0.5 (4.0) | 1 (1) | 0.7 (3.8) |
| Skull, Jugal, Incomplete Ossification | 4 (4) | 1.6 (12.0) | 4 (4) | 1.5 (9.1) |
| Skull, Parietals, Incomplete Ossification | 1 (1) | 0.5 (4.0) | 2 (2) | 0.7 (3.8) |
| Skull, Squamosal, Incomplete Ossification | 2 (2) | 0.6 (4.3) | 1 (1) | 0.7 (3.8) |
| Skull, Supraoccipital, Formed in Two Pieces | | | 1 (1) | 0.6 (4.0) |
| Skull, Supraoccipital, Incomplete Ossification | 4 (4) | 1.7 (13.0) | 6 (6) | 2.0 (11.5) |
| Sternum, Sternebra, Misaligned | 9 (8) | 1.6 (11.5) | 15 (15) | 2.6 (15.4) |
| Sternum, Sternebra, Not Ossified | 145 (67) | 21.5 (65.2) | 124 (73) | 16.3 (47.8) |
| Vertebral Column, Cervical Neural Arches, Incomplete Ossification | 2 (2) | 1.1 (8.7) | 2 (2) | 1.3 (7.7) |
| Vertebral Column, Cervical Neural Arches, Larger than Normal | | | 2 (1) | 1.0 (3.3) |

[1] Portage, Michigan Facility of Charles River Laboratories
[2] Definitive developmental toxicity studies exclusive of range-finding studies.

APPENDIX O
Protocol and Amendment

MPI
RESEARCH

# AN INHALATION DEVELOPMENTAL TOXICITY STUDY IN RATS WITH ANTIMONY TRIOXIDE

## TESTING FACILITY

MPI Research, Inc.
54943 North Main Street
Mattawan, MI 49071-9399 U.S.A.

## STUDY NUMBER

952-002

## STUDY DIRECTOR

Raymond E. Schroeder, M.S., D.A.B.T.

## SPONSOR

International Antimony Oxide Association
c/o Latham & Watkins
Suite 1300
1001 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2505

December 17, 2002

**Table of Contents**

# 1. INTRODUCTION

## 1.1. Study Number

952-002

## 1.2. Study Title

An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

## 1.3. Sponsor

International Antimony Oxide Association
c/o Latham & Watkins
Suite 1300
1001 Pennsylvania Ave., N.W.
Washington, D.C. 20004-2505

## 1.4. Sponsor Representative

Tessa L. Serex, Ph.D.

Telephone Number: 765-497-6637
Email: tserex@glcc.com

## 1.5. Objective

The objective of this study is to determine the developmental toxicity, including the teratogenic potential, of the test article in rats.

## 1.6. Experimental Design Overview

This study will consist of 3 treatment groups and 1 vehicle control group (receiving clean air under the same regimen) (26 mated females per group). Animals will be mated in-house to untreated males. The day on which evidence of copulation is observed will be considered Day 0 of gestation. The female rats will be exposed to the test article by nose-only inhalation, daily for 6 hours. Dosing will initiate on Day 0 of gestation and continue to and include Day 19 of gestation. Observations of dams will include clinical signs, gestational body weights and food consumption. Maternal lungs, nasopharyngeal tissue, and gross lesions will be collected and saved in formalin. Lung weights will be recorded. Additionally, blood will be collected from 10 randomly selected pregnant females per group at terminal necropsy and separated into a red blood cell (RBC) component and plasma. The RBC will be analyzed for total antimony levels and the plasma will be stored frozen for possible future evaluation. Litters will be delivered by cesarean section on Day 20 of gestation. Gravid uterine weight will be recorded. Total number of corpora lutea, implantations, early and late resorptions, live and dead fetuses will be recorded. Fetuses will be weighed, measured (crown-rump distance), and sexed externally. External abnormalities of fetuses will be recorded. Approximately one-half of the fetuses in each group will be examined for visceral abnormalities, and the remaining fetuses will be examined for skeletal abnormalities (bone and cartilage).

## 1.7. Regulatory Compliance

### 1.7.1. Test Guideline

This protocol meets or exceeds the draft guideline published in the United States Environmental Protection Agency Health Effects Test Guidelines, Inhalation Developmental Toxicity Study, OPPTS 870.3600, issued June 1996 and the OECD Guideline No. 414, Prenatal Developmental Toxicity Study (dated January 22, 2001).

### 1.7.2. Good Laboratory Practice

This nonclinical laboratory study will be conducted in accordance with the United States Environmental Protection Agency FIFRA Good Laboratory Practice Standards, 40 CFR Part 160, Toxic Substance Control Act Good Laboratory Practice Standards, 40 CFR Part 792, and OECD Principles of Good Laboratory Practice (C(81)30(Final)Annex 2).

## 1.8. Testing Facility

MPI Research, Inc.
54943 North Main Street
Mattawan, MI 49071-9399 U.S.A.

MPI Research is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

## 1.9. Computer Systems

The following are the proposed computer systems to be used during the conduct of this study. The actual systems and versions used will be documented in the final report.

| | |
|---|---|
| In-life System: | Provantis |
| Randomization: | Provantis |
| Developmental and Reproduction System: | Provantis |
| Pathology: | Provantis |
| Statistical Analyses: | SAS |
| Reporting: | SAS and Microsoft Office Professional |

## 1.10. Personnel

### 1.10.1. Study Director

Raymond E. Schroeder, M.S., D.A.B.T.

Telephone: 269-668-3336 ext. 215
Telefax: 269-668-4151
E-mail:ray.schroeder@mpiresearch.com

### 1.10.2. Alternate Contact

Paul E. Newton, Ph.D., D.A.B.T.

Telephone: 269-668-3336 ext. 230
Telefax: 269-668-4151
E-mail:paul.newton@mpiresearch.com

### 1.11. Proposed Study Schedule

| | |
|---|---|
| Study Initiation Date: | Date Study Director signs Study Approval-Initiation Line in this protocol |
| Experimental Start Date: | To be added by amendment |
| Experimental Termination Date: | To be added by amendment |
| Draft Report Mail Date: | To be added by amendment |

### 1.12. Quality Assurance

This study will be subjected to periodic inspections and the draft and final reports will be reviewed by the Quality Assurance Department of MPI Research in accordance with MPI Research's Standard Operating Procedures. Study quality assurance inspection records will be made available to the Sponsor Representatives during visits to MPI Research.

### 1.13. Alteration of Design

Alterations of this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, MPI Research will honor such change. However, written authorization will be obtained thereafter. All protocol modifications and the reasons will be documented, signed and dated by the Study Director and Sponsor. The protocol and all amendments will be issued to the Sponsor as well as at MPI Research.

### 1.14. Declaration of Intent

This study may be submitted to the U.S. E.P.A. and O.E.C.D. member countries.

## 2. TEST AND CONTROL ARTICLES

### 2.1. Description of Test Article

### 2.1.1. Identity

Antimony trioxide

A description, lot number, storage conditions, expiration date, safe handling procedures, as well as other relevant information will be documented in the study data.

### 2.1.2. Test Article Properties

The Sponsor will provide documentation on the strength, purity, composition, stability, physical properties, and other pertinent information on each batch of test article, unless

otherwise noted. If the Sponsor does not supply the above information (e.g. certificate of analysis), this will be listed as a GLP deviation in the final report.

### 2.2. Test Article Preparation

#### 2.2.1. Formulation

The test article will be used as received from the Sponsor and no adjustment will be made for purity. The test article will be administered neat (undiluted).

### 2.3. Reserve Sample

A reserve sample from each batch of test article used in this study will be taken and archived at MPI Research. If multiple studies are conducted with the same test article, a common reserve sample may be taken and labeled appropriately.

### 2.4. Test Article Disposition

Any remaining test article will be returned to the Sponsor after completion of the study. The test article will be returned to the address indicated in Section 1.3. unless otherwise indicated. The Sponsor will be notified prior to such shipment. Alternatively, MPI Research will dispose of the test article after completion of the study (additional cost).

## 3. TEST SYSTEM

### 3.1. Species

Rat

### 3.2. Strain

CD® [Crl: CD® (SD)IGS BR]

### 3.3. Source

Charles River Laboratories

### 3.4. Justification of Test System

The current state of scientific knowledge does not provide any acceptable alternatives, *in vitro* or otherwise, to the use of live animals to accomplish the purpose of this study. The rat is a universally used model for evaluating toxicity of various classes of chemicals and for which there is a large historical database.

### 3.5. Expected Age

The test females will be approximately 8-9 weeks of age at receipt and at least 9 weeks at initiation of mating. Males will be at least 8 weeks at receipt and 10 weeks at initiation of mating.

### 3.6. Expected Body Weight

The females will weigh approximately 190 to 250 grams at Day 0 of gestation. The actual body weight range may vary but will be documented in the data and final report. Animals outside this body weight range will be used at the discretion of the Study Director.

### 3.7. Number on Study

#### 3.7.1. Number Ordered

Males: 50

Females: 140 (nulliparous, virgin)

#### 3.7.2. Number on Study

Females: 104

#### 3.7.3. Justification for Number on Study

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards, and in consideration of applicable regulatory requirements.

#### 3.7.4. Selection for Study

Female rats will be given a clinical examination on the day of mating (Day 0 of gestation) and only animals considered suitable based on these examinations will be included in the selection process. Animals will be sorted into treatment groups using a standard block randomization procedure based on their Day 0 gestation body weights.

#### 3.7.5. Method of Identification

Each animal will be assigned an animal number to be used in Provantis and will be implanted with a microchip bearing a unique identification number. The individual animal number, implant number, and the MPI Research study number will comprise a unique identification for each animal. The animal's cage will be identified by the animal number, group, and sex.

#### 3.7.6. Final Disposition

Extra animals obtained for this study, but not placed on study, will either be transferred to the stock colony or euthanized and discarded. The final disposition of each animal will be documented in the study records.

#### 3.7.7. Euthanasia

Euthanasia will be by carbon dioxide inhalation unless specified otherwise. Euthanasia of fetuses/pups will be by intraperitoneal injection of sodium pentobarbital.

### 3.8. Husbandry

#### 3.8.1. Acclimation

Animals will be acclimated for at least 1 week prior to initiation of mating. During this period, animals will be observed daily for any clinical signs of disease. All animals will be given a detailed clinical examination prior to pairing with males. Animals with evidence of disease or physical abnormalities during acclimation will be euthanized and discarded.

#### 3.8.2. Housing

The animals will be individually housed in suspended, stainless steel, wire-mesh type cages except during pairing when animals will be housed 1:1 in the males cage.

### 3.8.3. Environmental Conditions

Fluorescent lighting will be provided via an automatic timer for approximately 12 hours per day. Temperature and humidity will be monitored and recorded daily and maintained to the maximum extent possible between 64 to 79° F and 30 to 70%, respectively.

### 3.8.4. Diet and Drinking Water

#### 3.8.4.1. Basal Diet

The basal diet will be meal Lab Diet® Certified Rodent Diet #5002, PMI Nutrition International, Inc. This diet will be available *ad libitum* unless designated otherwise. A single lot of diet will be used for the study. A sample of this diet will be collected and analyzed for total antimony. These analyses will be conducted by Chemical Solutions, Mechanicsburg, PA according to Good Manufacturing Practices. The lot number of the diet used on study will be identified in the study records.

#### 3.8.4.2. Basal Diet Contaminants

The Study Director is not aware of any potential contaminants likely to be present in the certified diet that would interfere with the results of this study. Therefore, other than total antimony, no other analyses from those routinely performed by the feed supplier will be conducted.

#### 3.8.4.3. Water

Tap water (supplied to the laboratory from the municipal water from Mattawan MI) will be supplied *ad libitum* to all animals via an automatic water system unless otherwise indicated.

#### 3.8.4.4. Water Contaminants

The drinking water used for the test animals will be monitored for specified contaminants at periodic intervals according to the testing facility's Standard Operating Procedures. Additionally, once during the study a sample of water from the animal study room will be collected and analyzed for total antimony. This analysis will be conducted by Chemical Solutions, Mechanicsburg, PA according to Good Manufacturing Practices. The Study Director is not aware of any potential contaminants likely to be present in the water that would interfere with the results of this study. Therefore, with the exception of total antimony, no analyses other than those mentioned previously in this protocol will be conducted.

### 3.9. Breeding Procedure

Female rats will be housed together with untreated male rats (1:1) used specifically for breeding. Males will be of the same strain and from the same source as the females. Mating will be established by daily inspection for a copulatory plug in the vagina or microscopic observation of sperm in the vaginal rinse. Evaluation of mating will be performed early each morning before 9:00 AM. The day evidence of mating is confirmed will be designated Day 0 of gestation. Once all mated females have been identified each day they will be sorted into groups as described previously. Females mated with the same males will be distributed to equalize as best possible distributions among the groups.

## 4. STUDY DESIGN

| | | NUMBER OF ANIMALS | | |
|---|---|---|---|---|
| | EXPOSURE LEVEL | INITIAL | LAPAROHYST-ERECTOMY/ NECROPSY | MICROSCOPIC PATHOLOGY |
| GROUP | mg/m$^3$ | F | F | F |
| 1 | 0 | 26 | 26 | A.R. |
| 2 | 1.5 | 26 | 26 | A.R. |
| 3 | 3.0 | 26 | 26 | A.R. |
| 4 | 6.0 | 26 | 26 | A.R. |

*A.R. = As Required (Study Director decision in consultation with the Sponsor)*

## 5. TEST AND CONTROL ARTICLE ADMINISTRATION

### 5.1. Route of Administration

The test article will be administered via nose-only inhalation exposures.

### 5.2. Justification for Route of Administration

The inhalation route is one of the potential routes of human exposure to this test article.

### 5.3. Frequency of Administration

The test article will be administered once per day for 6 hours.

### 5.4. Duration of Administration

Dosing will begin on Day 0 of gestation and continue through Day 19 of gestation.

### 5.5. Exposure Levels

0, 1.5, 3.0, and 6.0 mg/m$^3$

### 5.6. Justification of Exposure Levels

The exposure levels were selected by the Sponsor, or in consultation with the Sponsor, on the basis of available data from previous studies. Animals will be treated from fertilization (Day 0 of gestation) to Day 19, which is one day prior to scheduled euthanasia and laparohysterectomy (Day 20 of gestation). This dosing regimen is proposed to identify possible effects on preimplantation loss of the fertilized ova as well as effects on the developing fetus *in utero*.

### 5.7. Test Article Administration

The test article will be generated into the breathing air of the test animals. The test exposure atmosphere generation system employed will be determined during pre-study trials to determine the optimal equipment and operating conditions to generate accurate and precise exposure levels. The complete method will be described in the raw data and in the final report.

The nose-only exposure chambers will be operated at a minimum flow rate of 0.6 liters per minute per animal. This flow rate is considered adequate to maintain the oxygen level above 19%. One chamber will be used for each exposure level and the exposures will be conducted essentially concurrently.

### 5.8. Exposure Level Determination

#### 5.8.1. Nominal Concentration

A nominal exposure concentration will be calculated. The amount of test article consumed during the generation period will be divided by the total volume of air passing through the chamber (flow rate times generation duration) to give a nominal concentration.

#### 5.8.2. Analytical Concentration

Measurement of the exposure level will be performed at least once/exposure in the air control group and at least 4 times/exposure in the test article exposure groups using an appropriate sampling procedure and analysis by atomic absorption spectroscopy. The exact sampling method will be determined prior to initiation of animal exposures and documented in the raw data and final report.

### 5.9. Homogeneity

Prior to initiation of animal exposures, samples will be taken to show that the test article is evenly distributed from port to port on the nose-only chamber.

### 5.10. Chamber Trials

If more than the nominal amount of chamber trials is required because of test article generation or monitoring problems (2 weeks or 160 technician hours), the Sponsor will be consulted prior to any additional trialing (additional cost).

### 5.11. Particle Size Distribution Analyses

Particle size distribution analysis of the dust present in the exposure atmosphere will be determined at least once/day from each test article exposed group using a cascade impactor or other appropriate device.

### 5.12. Chamber Environment

The chamber environmental conditions will be maintained to the maximum extent possible at 20 to 24°C and 40 to 60% relative humidity. The exposure air flow, temperature, and relative humidity will be monitored continuously and recorded every 30 minutes.

### 5.13. Food and Water During Exposure Period

Food and water will be withheld during the exposures.

## 6. ANTEMORTEM STUDY EVALUATIONS

### 6.1. Cageside and Detailed Observations

All rats will be observed at least twice a day, 7 days a week, for morbidity, mortality, and signs of injury. Any findings will be recorded. Should mortality or other signs of toxicity be observed, these findings will be recorded on the day they are observed.

Daily from gestation days 0 through 20, each animal will be removed from the cage and given a detailed clinical examination. During the treatment period these examinations will be given as animals are removed from the exposure chambers. The first group of animals examined each day will be randomized each day of the exposure period.

### 6.2. Body Weights

Individual body weights will be recorded on Days 0, 3, 6, 9, 12, 15, 18, and 20 of gestation, and body weight change will be calculated for the following gestational day intervals; 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 0-20. Adjusted Day 20 gestation body weights (actual Day 20 gestation body weight minus the gravid uterine weight) and adjusted body weight gain (Days 0-20 of gestation) will also be calculated and reported.

### 6.3. Food Consumption

Food consumption will be recorded on the corresponding body weight days and calculated for the following intervals; Days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 0-20 of gestation.

### 6.4. Clinical Pathology

Blood samples (as much as possible) will be collected via cardiac puncture from 10 randomly selected pregnant animals per group on Day 20 of gestation. These samples will be separated into RBC and plasma components. The RBC will be analyzed for concentration of bound antimony. The RBC samples will be refrigerated at 2°- 8°C and shipped for analysis. Samples will be sent to:

Ela Bakowska,
National Medical Services
3701 Welsh Road
Willow Grove, PA 19090
Phone Number 215-366-1283
Fax Number: 215-657-2972

The plasma samples will be stored frozen (-20° C) until it is determined that these analyses are not required. The Sponsor will be notified concerning this decision following review of the RBC analytical results.

All analytical work will be conducted by National Medical Services (NMS), Willow Grove, Pennsylvania using an analytical method developed by NMS. The work performed in conjunction with this study will be conducted in compliance with GLPs and subject to review by the Quality Assurance Unit (QAU) of that laboratory. The findings of their QAU will be submitted to the MPI Study Director and Management. Method validation for antimony on the ICP/MS will be conducted using rat control RBCs. A tabular presentation of RBC antimony levels and a Quality Assurance Statement will be provided to MPI for inclusion as an appendix in the main study final report.

### 6.5. Moribundity

Any animal showing signs of severe debility or toxicity, particularly if death appears imminent, will be euthanized for humane reasons, and to prevent the loss of tissues through autolysis, using the anesthesia method as described under Euthanasia in the Test System portion of this protocol. All animals euthanized *in extremis* or found dead will be subjected to a necropsy as described in the Postmortem Study Evaluations section. The disposition of these animals and intact fetuses or pups is described in the Teratologic Examinations section.

### 6.6. Premature Delivery

Females showing signs of premature delivery ***within 1 day*** of scheduled euthanasia will be subjected to a laparohysterectomy and necropsy (see Postmortem Study Evaluations section). The fetuses will be subjected to a teratologic examination (see Teratologic Examinations section). Uterine implantation data for these females will be reported but not included in statistical analysis with the scheduled Day 20 gestation data. Dams that deliver, die, or are euthanized ***earlier than 1 day*** before scheduled euthanasia will also be subjected to a uterine and ovarian examination. Fetuses from these dams will be examined externally to the fullest possible extent and placed in 10% neutral buffered formalin for possible future examination.

## 7. POSTMORTEM STUDY EVALUATIONS

A complete necropsy will be performed under procedures approved by a veterinary pathologist on the following animals.

1. Dams found dead
2. Dams euthanized *in extremis*
3. Dams showing signs of premature delivery ***within 1 day*** of scheduled euthanasia
4. Dams euthanized at termination of the study

Special emphasis will be placed on structural abnormalities or pathologic changes which may have influenced the pregnancy.

A laparohysterectomic examination (see Uterine and Ovarian Examinations section) will be conducted on all dams that die, initiate delivery, or are euthanized ***in extremis***. Fetuses from these dams will be evaluated as directed in the section entitled Teratologic Examinations.

Lungs, nasopharyngeal tissue, and gross lesions and/or target organs from the dams will be saved in 10% neutral buffered formalin for possible future microscopic evaluation. The lungs and brain will be weighed and the lungs then infused via the trachea with formalin. The brain weight will be used to calculate a lung/brain weight ratio but the brain will not be saved unless associated with a gross lesion. Carcasses will be discarded.

### 7.1. Uterine and Ovarian Examinations

On Day 20 of gestation, each female will be euthanized and immediately subjected to a laparohysterectomy. The skin will be reflected from a ventral midline incision to examine mammary tissue and locate any subcutaneous masses. The abdominal cavity will be opened, and the uterus will be exposed. The uterus will be excised, the gravid uterine weight will be recorded, and the fetuses will be removed. Beginning at the distal end of the left uterine horn, the location of viable and nonviable fetuses, early and late resorptions for each uterine horn, position of the cervix, and the number of total implantations and corpora lutea will be recorded. The embryonic membrane of each fetus will be gently removed, and each fetus will be pulled away from the placenta, fully extending the umbilical cord. The placentae will be grossly examined.

Each implant will be categorized according to the following criteria:

- Viable fetus - responds to touch

- Nonviable fetus - does not respond to touch, no signs of autolysis
- Late resorption - recognizable fetal form, but undergoing autolysis
- Early resorption - implantation site, tissue has no recognizable fetal characteristics

Uteri from females that appear nongravid will be opened and placed in 10% ammonium sulfide solution for detection of implantation sites[1]. If no foci are seen, the female will be considered not pregnant and summary data will be deleted from all data sets for these individuals. If foci are seen, the female will be considered pregnant, the foci will be considered to be early resorptions, and these data will be included in the calculation of uterine implantation data.

A necropsy will be conducted on each animal as described in the Postmortem Study Evaluations section. Maternal lungs, nasopharyngeal tissue, gross lesions and/or target organs will be saved in 10% neutral buffered formalin for possible microscopic examination (Sponsor decision and additional cost consideration). The lungs will be weighed and then infused via the trachea with formalin. The brain will also be weighed to determine a lung/brain weight ratio but only saved if associated with a gross lesion. Collection of gross lesions and/or target organs from treated animals will necessitate collection of sufficient corresponding tissues from controls for comparison purposes, if necessary. Possible histopathologic examination of lesions and/or target organs will be performed as deemed necessary by the Study Director in consultation with the Sponsor. The carcasses will be discarded.

### 7.2. Teratologic Examinations

Fetuses will be individually weighed, measured (crown-rump distance), sexed, tagged and examined for external malformations and variations. Approximately one-half of the fetuses in each litter will be placed in Bouin's solution for subsequent soft tissue examination using the Wilson razor-blade sectioning technique.[2] The remaining fetuses will be fixed in alcohol, processed for Alizarin Red S and Alcian blue staining, and cleared with glycerin for subsequent skeletal examination of bone and cartilage.[3] Fetal findings will be classified as malformations or developmental variations under the supervision of a developmental toxicologist.

Intact fetuses from dams that die or are euthanized ***within 1 day*** of scheduled euthanasia will be evaluated as specified above. Intact fetuses from dams that die or are euthanized ***in extremis*** prior to Gestation Day 19 will be examined externally when possible and preserved in 10% neutral buffered formalin at the discretion of the Study Director. All other tissues from these females will be examined and discarded unless deemed necessary for confirmation of other findings.

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[1] Kopf, R., Lorenz, D., and Salewski, E. (1964). The effects of thalidomide on the fertility of rats studied in two generations. *Naunyn Schmiedebergs Arch. Pharmacol.* **247**, 121-135.

[2] Wilson, J. G. (1965). Methods for administering agents and detecting malformations in experimental animals. J. G. Wilson and J Warkany, eds. *Teratology-Principles and Techniques*. The University of Chicago Press, Chicago, Illinois, pp. 262-277.

[3] Kimmel, C.A. and Trammell, C. (1981). A rapid procedure for routine double staining of cartilage and bone in fetal and adult animals. *Stain Technology*, **56**, 271-273.

## 8. STATISTICS

The following is the proposed analysis plan. If any other techniques are used (Sponsor consulted), they will be documented in the final report.

**Table of Statistical Comparisons**

| Control Group | Treatment Groups |
|---|---|
| 1 | 2, 3, 4 |

The above table defines the set(s) of comparisons to be used in the statistical analyses described below. If more than one set of comparisons is required, all analyses will be conducted separately on each set unless stated otherwise.

| Endpoint | Analysis |
|---|---|
| **Parental In-life Data** | |
| Gestation Body Weights | Group Pair-wise Comparisons |
| Gestation Body Weight Changes | Group Pair-wise Comparisons |
| Gestation Food Consumption | Group Pair-wise Comparisons |
| Adjusted Body Weights | Group Pair-wise Comparisons |
| Adjusted Body Weight Changes (Days 0-20) | Group Pair-wise Comparisons |
| RBC antimony levels | Group Pair-wise Comparisons |
| | |
| **Fertility Indices** | |
| Pregnancy Index | Fisher's Exact Test |
| | |
| **Pathology** | |
| Absolute lung and brain weights and lung weights relative to brain weights | Group Pair-wise Comparisons |
| | |
| **Uterine and Ovarian Exam** | |
| Gravid Uterine Weights | Group Pair-wise Comparisons |
| Corpora Lutea/dam | Group Pair-wise Comparisons |
| Total Implantations/dam | Group Pair-wise Comparisons |
| Fetal Sex Ratio (% males/litter) | Arcsin Square-Root Transformation |
| Litter Size/dam | Group Pair-wise Comparisons |
| Viable Fetuses/dam | Group Pair-wise Comparisons |
| Nonviable Fetuses/dam | Descriptive Statistics |
| Total Number Resorptions/dam | Group Pair-wise Comparisons |
| Number Early Resorptions/dam | Group Pair-wise Comparisons |
| Number Late Resorptions/dam | Group Pair-wise Comparisons |
| % Preimplantation Loss | Arcsin-Square-Root Transformation |
| % Postimplantation Loss | Arcsin-Square-Root Transformation |
| Mean Fetal Body Weights | Covariate Analysis |
| Mean Crown-rump Distance | Group Pair-wise Comparisons |

| Endpoint | Analysis |
|---|---|
| Individual Malformations by finding and exam type (external, visceral, and skeletal)-litter incidence[a] | Fisher's Exact Test |
| Individual Variations by finding and exam type (external, visceral, and skeletal)-litter incidence[a] | Fisher's Exact Test |
| Total Malformations (external, visceral, and skeletal combined)-litter incidence[a] | Fisher's Exact Test |

[a]Fetal and litter incidences will be reported, but only the litter incidences will be statistically analyzed.

### 8.1. Group Pair-Wise Comparisons

For each specified endpoint (see table above) and for all collection intervals, Levene's test[4] will be used to assess homogeneity of group variances. If Levene's test is not significant ($p \geq 0.01$), Dunnett's test[5] will be used to compare each treatment group with the control group. If Levene's test is significant ($p < 0.01$), comparisons with the control group will be made using Welch's t-test[6] with a Bonferroni correction. Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

### 8.2. Arcsin-Square-Root Transformation

Data comprised of percent values will be transformed using the arcsin of the square root[7]. The analysis described in the Group Pair-Wise Comparison paragraph will be used to analyze the transformed percentage values.

### 8.3. Fisher's Exact Test

Each treatment group will be compared to the control group using a Fisher's exact test with a Bonferroni correction. Results will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

### 8.4. Covariate Analysis

For each endpoint (mean of fetal body weights), a test of assumptions[8] for Analysis of Covariance will be done to determine whether the litter size will be included as a covariate in the model. If the assumptions on the Analysis of Covariance are met, the model with the covariate will be used to test for a difference from control using the Dunnett's test[5]. If the

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[4] Milliken, G.A. and Johnson, D.E. (1992). *Analysis of Messy Data*. Chapman and Hall, London.

[5] Dunnett, C.W. (1955). A multiple comparison procedure for comparing several treatments with a control. *Journal of the American Statistical Association* **56**, 52-64.

[6] Welch, B.L. (1937). The significance of difference between two means when the population variances are unequal. *Biometrika* **29**, 350-362.

[7] Steel, R.G.D. and Torrie, J.H. (1980). *Principles and Procedures of Statistics. A Biometrical Approach.* McGraw-Hill, New York.

[8] Littell, R.C., Milliken, G.A., Stroup, W.W., and Wolfinger, R.D. (1996), *SAS System for Mixed Models.* SAS Institute Inc., Cary, NC.

assumptions for the Analysis of Covariance are not met, the endpoint will be analyzed in the manner described in the Group Pair-wise Comparisons section.

Whether the covariate is included or not, LSMEANS, which are the adjusted means, will be displayed on the summary table. If the covariate is used in the analysis, these adjusted means can be used to help in interpretation of the analysis.

Each treatment group will be compared with the control group and results will be reported at the 0.05 and 0.01 significance levels. Endpoints will be analyzed using two-tailed tests unless indicated otherwise.

### 8.5. Descriptive Statistics

Descriptive statistics will consist of means, standard deviations, and group size for each group and time period.

## 9. STUDY REPORTS

### 9.1. Progress/Status Reports

A progress report will be submitted to the Sponsor following the maternal necropsies, which will include a summary of maternal data (body weights, food consumption, clinical findings, corpora lutea, and uterine implantations) and fetal data (body weights, crown-rump distance, and external findings).

### 9.2. Final Report

After completion of the study, a comprehensive draft report containing the results of all tests, analyses, observations and measurements required by this protocol and an interpretative summary of the study results will be submitted to the Sponsor. The report will include all items required by the applicable regulatory agency. After receipt of any Sponsor comments, 2 copies (1 bound and 1 unbound) of the final report will be issued.

Six months after issuance of the draft report, if no requested revisions or instructions to finalize have been communicated by the Sponsor, the draft report will be issued as a final report, signed by the Study Director, and submitted to the Sponsor. Any modifications or changes to the draft report requested 6 months after issuance of the draft will be performed at additional cost to the Sponsor.

## 10. DATA AND SPECIMEN RETENTION

All raw data, documentation, records, protocol, reserve samples, specimens (slides, blocks, and wet tissues), and the final report generated as a result of this study will be retained at MPI Research, or an approved archive facility contracted by MPI Research, for a period of 1 year following completion of the study (final report issue date). Retention of materials after the time stated above will be subject to a future contractual agreement between the Sponsor and MPI Research.

## 11. ANIMAL WELFARE

MPI Research is committed to complying with all applicable regulations governing the care and use of laboratory animals. Animal welfare for this study will be in compliance with the

U.S. Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2 and 3). The Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Academy Press, Washington, D.C., 1996, will be followed. This facility maintains an Animal Welfare Assurance statement with National Institutes of Health Office of Laboratory Animal Welfare.

In order to ensure compliance:

A. This protocol will be reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) before the initiation of treatment.

B. The Sponsor, by his or her signature, attests that the activities specified in this protocol do not unnecessarily duplicate any previous experiment. Since this is part of a safety evaluation program required by the relevant supervising government agency cited in this protocol, it is not considered to provide exactly the same information as any other study conducted with the same test article.

C. The Study Director has reviewed resources for alternatives to procedures that may cause more than momentary or slight pain or distress to the animal and has signified that (select one):

___X__ i) The relevant supervisory government agency currently give no alternatives.

_____ ii) A literature search has been performed to determine whether an alternative procedure which reduces pain or distress is available and none were found (identify information sources used below).

Date:
Interval Searched:
Search terms:
Database(s) searched:

_____ iii) This study does not require any procedures that may cause more than momentary or slight pain or distress to the animal. Note, unknown test articles are presumed to have the potential to cause more than slight pain or distress.

D. The Study Director has determined that the withholding of agents such as analgesics or sedatives (unless specified in this protocol) is justified for scientific reasons. The purpose of the study is to provide some side effects in animals at least in the high dose under study. Regulations and standards of government agencies require that the affected animals remain on study unless in severe (or chronic) pain and or otherwise moribund.

## 12. SIGNATURES

### 12.1. Sponsor Approval

Tessa L. Serex, Ph.D.
Sponsor Representative

12-20-02
Date

### 12.2. Study Director Approval/Study Initiation

Raymond E. Schroeder M.S., D.A.B.T.
Study Director

12/20/02
Date

MPI Research Study Number: 952-002

MPI RESEARCH

International Antimony Oxide Association

Title: An Inhalation Developmental Toxicity Study in Rats with Antimony Trioxide

Protocol Amendment No. 1



| Item | Revision or Clarification |
|---|---|
| 1. | 1. INTRODUCTION<br>1.11. Proposed Study Schedule<br>Add the following dates:<br>Experimental Start Date: February 25, 2003<br>Experimental Termination Date: March 30, 2003<br>Draft Report Mail Date: July 29, 2003 |
| 2. | 6. ANTEMORTEM STUDY EVALUATIONS<br>6.4 Clinical Pathology:<br>Add that blood will be collected with EDTA anticoagulant. |

| Item | Justification |
|---|---|
| 1. | Confirms study dates to be addressed by amendment. |
| 2. | Confirms anticoagulant to be used for collection of RBC and plasma. |

Approved by:

Tessa L. Serex — 3-10-03

Tessa L. Serex, Ph.D.
Sponsor Representative

Date

Raymond E. Schroeder — 3/17/03

Raymond E. Schroeder, M.S., D.A.B.T.
Study Director

Date

# APPENDIX P
Deviations

## DEVIATIONS

This study was conducted in conformance with the protocol, except for the following deviations.

A simple randomization was used to place animals on study, instead of a block, as specified by the protocol, due to the uneven number of animals available for placement each day.

On March 17 and 18, 2003, the volume of blood collected for RBC analysis was not documented.

Due to the test article and type of generation system used, the humidity in the exposure chamber was significantly lower than the protocol-specified range of 40 to 60%. The actual range was between 2 to 14%. On numerous occasions, the temperature in the exposure chamber was outside the protocol-specified range of 20 to 24°C. The actual range was between 18 to 24°C.

External observations for two fetuses from one litter at 6.3 $mg/M^3$ (litter number 396, fetus numbers 6 and 9) were not documented.

The brain weight for one control female (animal number 321) was not documented.

In the opinion of the Study Director, these minor deviations did not affect the quality or integrity of the study.

**Final report**

**Dustiness and particle size testing of eight Diantimony trioxide samples**

**EBRC Consulting GmbH**
**Hannover, 01.11.2005**
**(Dr. R. V. Battersby)**

Issue: Assessment of dustiness and particle size distributions of eight diantimony trioxide samples with a perspective to the composition of workplace aerosols

Samples:
- No. 1: Diantimony trioxide “Campine Z”
- No. 2: Diantimony trioxide “Campine N”
- No. 3: Diantimony trioxide “GLCC Microfine AO3”
- No. 4: Diantimony trioxide “Triox Blue”
- No. 5: Diantimony trioxide “ATO Sica 1”
- No. 6: Diantimony trioxide “ATO Sica 2”
- No. 7: Diantimony trioxide “ATO Sica 3”
- No. 8: Diantimony trioxide “Antimony Trioxide - V”

**EBRC Consulting GmbH**
Zeppelinstr. 8
D - 30175 Hannover
Germany

## 1. Introduction

Eight samples of diantimony trioxide (DAT) representing the range of commercially available particle sizes were initially subjected to total particle size analysis (Malvern Mastersizer, dry powder feeder), with the aim of deriving a characteristic d50 value for the "total material". It is expressly noted that the values derived from these measurements do not necessarily match with those stated in product specification sheets, where particle sizes are given which result from the use of techniques such as ultra-sonification, liquid immersion etc. which are intended to break up any aggregates, but also methods that may be considered specific only for DAT. In consequence, such other testing results are more relevant to predict particle behaviour under technical/industrial use, but not adequate for prediction of inhalation exposure under occupational circumstances.

"Physical" particle size distributions do not necessarily reflect the particle size of aerosols that may be formed under practically relevant workplace conditions, for example during manual operations such as bag filling and emptying, or under mechanical agitation as in mixing and weighing operations. For this reason, the particle size distribution of the airborne fraction generated during mechanical agitation in the rotating drum method acc. to Heubach was determined.

Such particle size distribution data has previously been used successfully within an EU Risk Assessment (Zinc and Zinc compounds) for extrapolation within similar substances, and also in predicting particle-size dependant deposition behaviour in the respiratory tract (Battersby & Boreiko, 2004). A similar approach has been used in the recent Voluntary Risk Assessment on Lead and Lead compounds, submitted to TCNES review in May 2005

The Heubach method also provides a "total dustiness" indicating the propensity of a material to become airborne, and thus serving as an indicator of the mobility under workplace conditions that may be utilised in selecting suitable analogies to other chemical substances with respect to their dermal loading.

Finally, the relative density of a representative sample of DAT was determined under GLP and according to EU method A.3 and OECD 109, since this parameter is relevant for the conversion between physical particle size and aerodynamic diameter.

## 2. Description of test material

### 2.1 Campine Z

| | |
| --- | --- |
| Test item: | Antimony Trioxide “Campine Z” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | Campine NV, Nijverheidsstraat 2, B-2340 Beerse, Belgium |
| Batch no.: | 27567 |
| Purity: | 99.88 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, November 17, 2004, Campine NV, Nijverheidsstraat 2, B-2340 Beerse, Belgium |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 11/2009 (confirmed by producer) |

### 2.2 Campine N

| | |
| --- | --- |
| Test item: | Antimony Trioxide “Campine N” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | Campine NV, Nijverheidsstraat 2, B-2340 Beerse, Belgium |
| Batch no.: | 29113 |
| Purity: | 99.93 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, November 17, 2004, Campine NV, Nijverheidsstraat 2, B-2340 Beerse, Belgium |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 11/2009 (confirmed by producer) |

### 2.3 GLCC Microfine® AO3

| | |
| --- | --- |
| Test item: | Antimony Trioxide “GLCC Microfine AO3” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | Great Lakes Chemical Corporation de Mexico, S.A. de CV, Ave EL Pasito No 4000, Reynosa, TMS, Mexico 88710 |
| Batch no.: | 0000021298 |
| Purity: | 99.87 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, December 06, 2004, Great Lakes Chemical Corporation de Mexico, S.A. de CV, Ave EL Pasito No 4000, Reynosa, TMS, Mexico 88710 |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | until 02/2007 (confirmed by producer) |

### 2.4 Triox Blue (PDC Lucette)

| | |
| --- | --- |
| Test item: | Antimony Trioxide “Triox Blue” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | Produits Chimiques de Lucette, Z.I. de la Vallée Verte, B.P. 1<br>F-53940 Le Geneste Saint Isle, France |
| Batch no.: | 649003 |
| Purity: | 99.78 % |
| Physical state: | powder, white |
| Certificate no.: | Analytical Certificate Ref: 6652, printed March 24, 2005;<br>Produits Chimiques de Lucette, Z.I. de la Vallée Verte, B.P. 1<br>F-53940 Le Geneste Saint Isle, France |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 2 years, until 03/2007 (confirmed by producer) |

### 2.5 ATO Sica 1

| | |
| --- | --- |
| Test item: | Antimony Trioxide “ATO Sica 1” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Batch no.: | 04I18L3 BB2 (sample 1) |
| Purity: | 99.8 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, printed March 25, 2005;<br>S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 03/2010 (confirmed by producer) |

### 2.6 ATO Sica 2

| | |
| --- | --- |
| Test item: | Antimony Trioxide “ATO Sica 2” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Batch no.: | 04H19L3 BB7 á 28 (sample 2) |
| Purity: | 99.8 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, printed March 25, 2005;<br>S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 03/2010 (confirmed by producer) |

### 2.7 ATO Sica 3

| | |
| --- | --- |
| Test item: | Antimony Trioxide “ATO Sica 3” |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Batch no.: | 2/9 (sample 3) |
| Purity: | 99.8 % |
| Physical state: | powder, white |
| Certificate no.: | Certificate of Analysis, printed March 25, 2005;<br>S.I.C.A., Rue Géo Lufbéry, F-2301 Chauny, France |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 03/2010 (confirmed by producer) |

### 2.8 Antimony Trioxide –V

| | |
| --- | --- |
| Test item: | Antimony Trioxide – V |
| Chemical name: | Diantimony Trioxide |
| CAS-No.: | 1309-64-4 |
| Empirical formula: | $Sb_2O_3$ |
| Molecular mass: | 291.52 g/mol |
| Producer: | Coplosa S.A., Sector E, Zona Franca, E-08040 Barcelona, Spain |
| Batch no.: | V50/MO/SB-200 |
| Purity: | 99.7 % |
| Physical state: | powder, white |
| Certificate no.: | undated quality certificate supplied with the test item in march 2005 by<br>Coplosa S.A., Sector E, Zona Franca, E-08040 Barcelona, Spain |
| Storage conditions: | Ambient temperature in tightly closed container |
| Stability: | 5 years, until 03/2010 (confirmed by producer) |

## 3. Methods

### 3.1 Determination of relative density

The determination of rel. density was performed representatively on one sample of DAT („Campine N“) according to the consolidated version of Council Directive 67/548/EEC Annex V, Part A: Methods for the determination of physico-chemical properties. A.3. Relative Density (Smeykal, 2005) with the aid of a gas comparison pycnometer. The volume of the test item was measured in air in a cylinder of variable calibrated volume. For the calculation of density, a mass measurement is taken after concluding the volume measurement. The relative density $D_4^R$ is calculated according to the following equation

$$D_4^R = \frac{\rho_{PR}}{\rho_{W4}}$$

$D_4^R$: Relative density (without dimension) measured at ambient temperature R compared to the density of water at 4 °C

$\rho_{PR}$: Density of the test item measured at ambient temperature R in g/cm³

$\rho_{W4}$: Density of water at 4 °C ( = 1.000 g/cm³)

Remark: in the dustiness reports issued by the test facility (DMT, see Appendices), the relative densities given by the producers and also stated in table 2 were used for correction between physical particle size and aerodynamic diameter. However, any further recalculations should be based on this parameter in view of the relevance of the study (guideline-conform study conduct under GLP).

### 3.2 Total particle size testing

The total particle size distribution measurements involved a dry dispersion technique with laser-diffraction measurement, in accordance with the following guidelines:

OECD 110: Particle Size Distribution,
CIPAC MT 187: Particle Size Analysis by Laser Diffraction,
ISO13320-1: Particle Size Analysis - Laser Diffraction Methods.

The test procedure and underlying principles can briefly be described as follows:

- coarse particles are separated from fines by sieving at a mesh size 125 µm, where required.
- the particle size distribution of the fines is determined by laser diffraction. The particles are introduced to the analyser beam by a dry powder feeder by direct spraying into the measurement chamber. The particle size distribution is derived from the recorded diffraction pattern.
- the test item is fed to the dry powder feeder, loosened by an integrated vibrator. The particles are then dispersed and fed to the optical system by pressurised air at 1.5 $bar_g$, and after passing the spectrometer the sample is collected in a cyclone.
- the average of two measurements is reported as the final result.

### 3.3 Dustiness testing

In dustiness tests with the Heubach-Method, the test material is introduced into a rotating drum apparatus, a test design intended to simulate mechanical stress under conditions of industrial processes involving handling/manipulation of these materials. Any dust thus generated is conveyed in a stream of air to a collection chamber, where it is precipitated and determined gravimetrically. The test result is expressed in “mg/g” of dust/sample. However, in the modified Heubach-Method (acc. to DMT), the generated dust is not collected as a “bulk” sample, but in fact separated in a cascade impactor, which allows a discrimination of the generated dust particles according to particle sizes. The particle size distribution can be recalculated from the aerodynamic diameter ($d_a$, i.e. the cut off points of the impactor stages) to the physical particle diameter $d_p$ with the following formula, by correcting for the particle density $\rho_p$ (Willeke, 1993):

$$d_p = \frac{d_a}{\sqrt{\rho_p}}$$

It is noted that this conversion via rel. density is only required where a recalculation from aerodynamic diameters to physical particle size is required. However, the conclusions in this report are based on aerodynamic diameters as reported in the dustiness tests.

## 4. Results

### 4.1 Results: Determination of relative density

The relative density of the test item “Campine N” was determined according to the method described in section 3.1 of this document. As the final result, the relative density (compared to water at 4°C) is given as $D_4^R$ = 5.90 (Smeykal, 2005).

### 4.2 – Total particle size of eight different diantimony trioxide samples

The physical particle size distribution was determined by the method described in subchapter 3.2 above for eight different grades of test material which were also used subsequently in the dustiness testing. The results are presented in the following graph (zinc oxide included only for comparative purposes).

It is interesting to note that except for the two samples with the highest median physical particle size (ATO Sica 3 and Campine Z), all other samples show bimodal distributions. This can only be explained by a high tendency of agglomeration, relating to fractions of less than 25 % (mass) of total material, consisting of aggregates with d50 values between 200 and 300 µm.

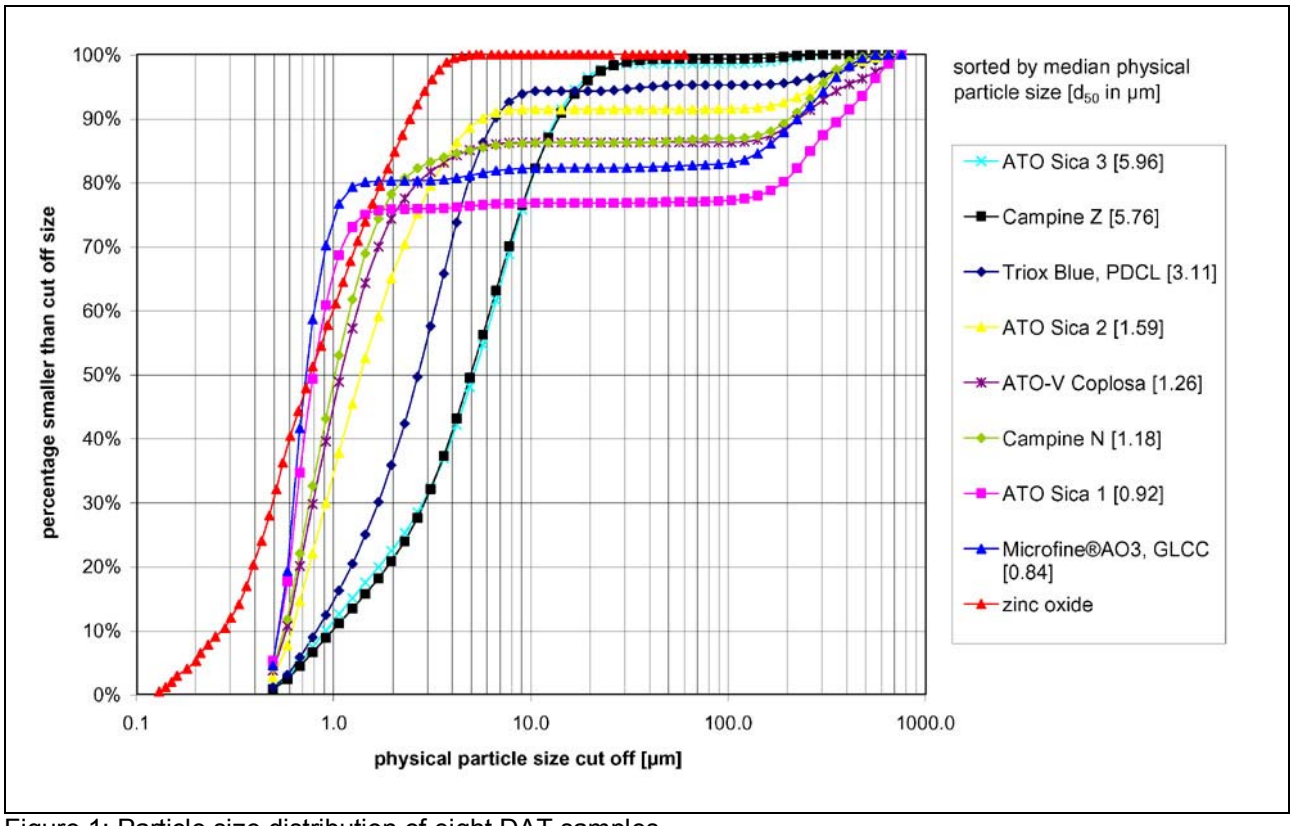


Figure 1: Particle size distribution of eight DAT samples

An explanation for the particle aggregation phenomenon observed for DAT can not be reasonably derived from the graphical presentation on the previous page (Figure 1).

For this reason, the relative percentage of aggregates above 100 µm in each test material was plotted against the median (d50) physical particle size, as shown in Figure 2 below. For ease of interpretation, the same colour and symbol code as in the previous graph has been applied.

It can be seen that the fraction of aggregates decreases with particle size. One apparent interpretation would be that with decreasing particle sizes, the surface of particles in relation to their volume increases, and thus may enhance aggregation via adhesion.

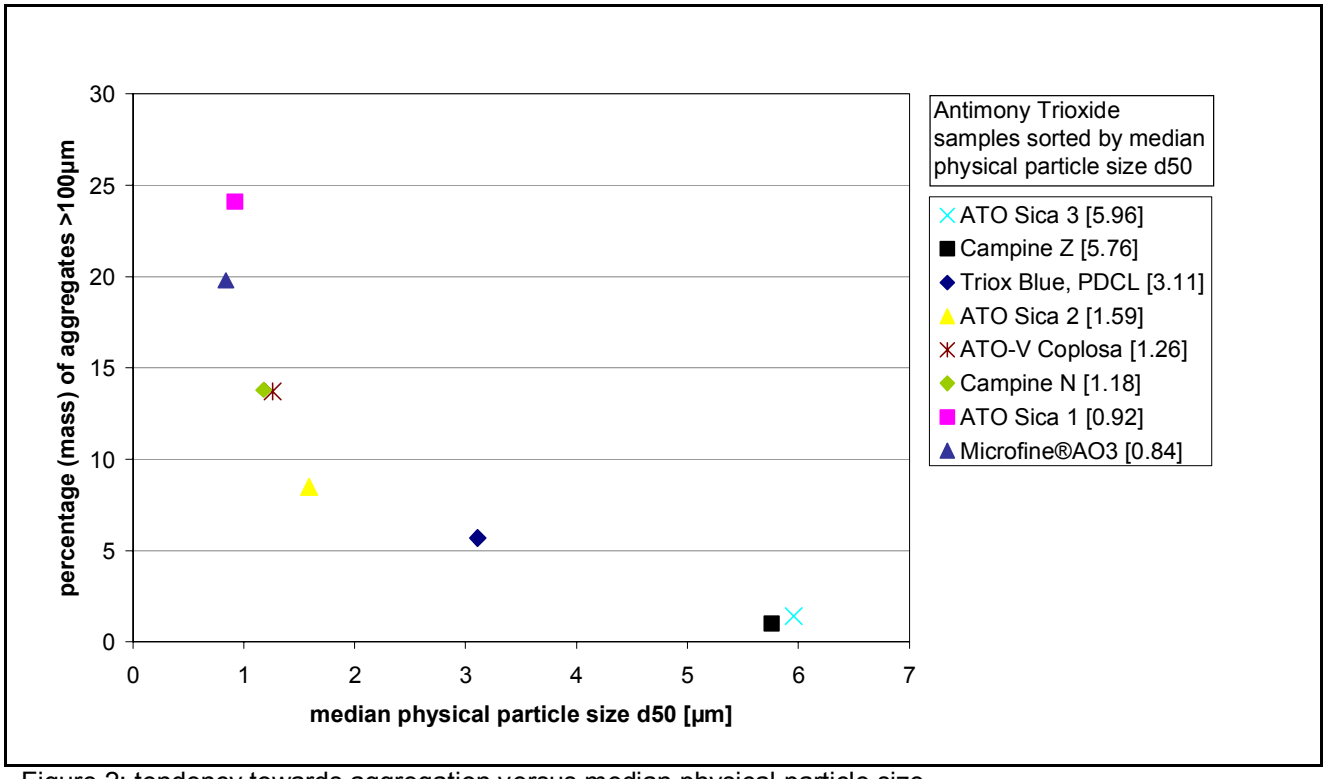


Figure 2: tendency towards aggregation versus median physical particle size

### 4.3 Dustiness and particle size distributions of dust generated in the Heubach dust meter

For all eight sample described above, total dustiness and particle size of the fraction of material that becomes airborne under the conditions of this test (determined according to the method described under subchapter 3.3) are given in the table below. Data for zinc oxide is given for comparative purposes only.

Table 1: total dustiness and particle size distribution of the airborne fraction, diantimony trioxide

| | cumulative particle size distribution (%age larger than cut off) | | | |
|---|---|---|---|---|
| cut off [µm] | Campine Z[(1)] | Campine N[(1)] | GLCC Microfine AO3[(1)] | Zinc oxide[(2)] |
| 0.473 | 99.90 | 98.69 | 99.78 | 99.96 |
| 0.989 | 99.58 | 94.28 | 99.04 | 99.84 |
| 2.04 | 98.48 | 83.25 | 96.19 | 98.10 |
| 4.06 | 95.57 | 48.53 | 86.72 | 93.14 |
| 8.13 | 89.88 | 10.47 | 76.11 | 84.53 |
| 15.8 | 68.46 | 5.45 | 70.88 | 73.92 |
| 32.4 | 35.69 | 5.01 | 63.51 | 60.02 |
| | | | | |
| total dustiness [mg/g] | 294.42 | 10.91 | 35.97 | 30.06 |

| | cumulative particle size distribution (%age larger than cut off) | | | | |
|---|---|---|---|---|---|
| cut off [µm] | Triox Blue[(3)] | ATO Sica 1[(3)] | ATO Sica 2[(3)] | ATO Sica 3[(3)] | Antimony Trioxide -V[(3)] |
| 0.473 | 99,67 | 99,55 | 99,34 | 99,83 | 99,26 |
| 0.989 | 98,57 | 98,02 | 97,11 | 99,26 | 96,75 |
| 2.04 | 96,08 | 90,22 | 90,85 | 98,45 | 86,41 |
| 4.06 | 88,32 | 63,89 | 66,83 | 96,58 | 52,39 |
| 8.13 | 73,51 | 41,75 | 36,13 | 93,17 | 7,82 |
| 15.8 | 50,04 | 35,03 | 20,81 | 72,41 | 4,61 |
| 32.4 | 28,27 | 31,79 | 14,55 | 35,57 | 4,51 |
| | | | | | |
| total dustiness [mg/g] | 145,48 | 81,49 | 39,81 | 178,80 | 18,05 |

Sources: (1) Weidenfeller, 2005; (2) Armbruster, 2000; (3) Weidenfeller, 2005a

Based on the raw data above (aerodynamic diameters) which was extracted from the original reports on dustiness/PSD, the following cumulative distribution is presented graphically, with zinc oxide included for comparative purposes:

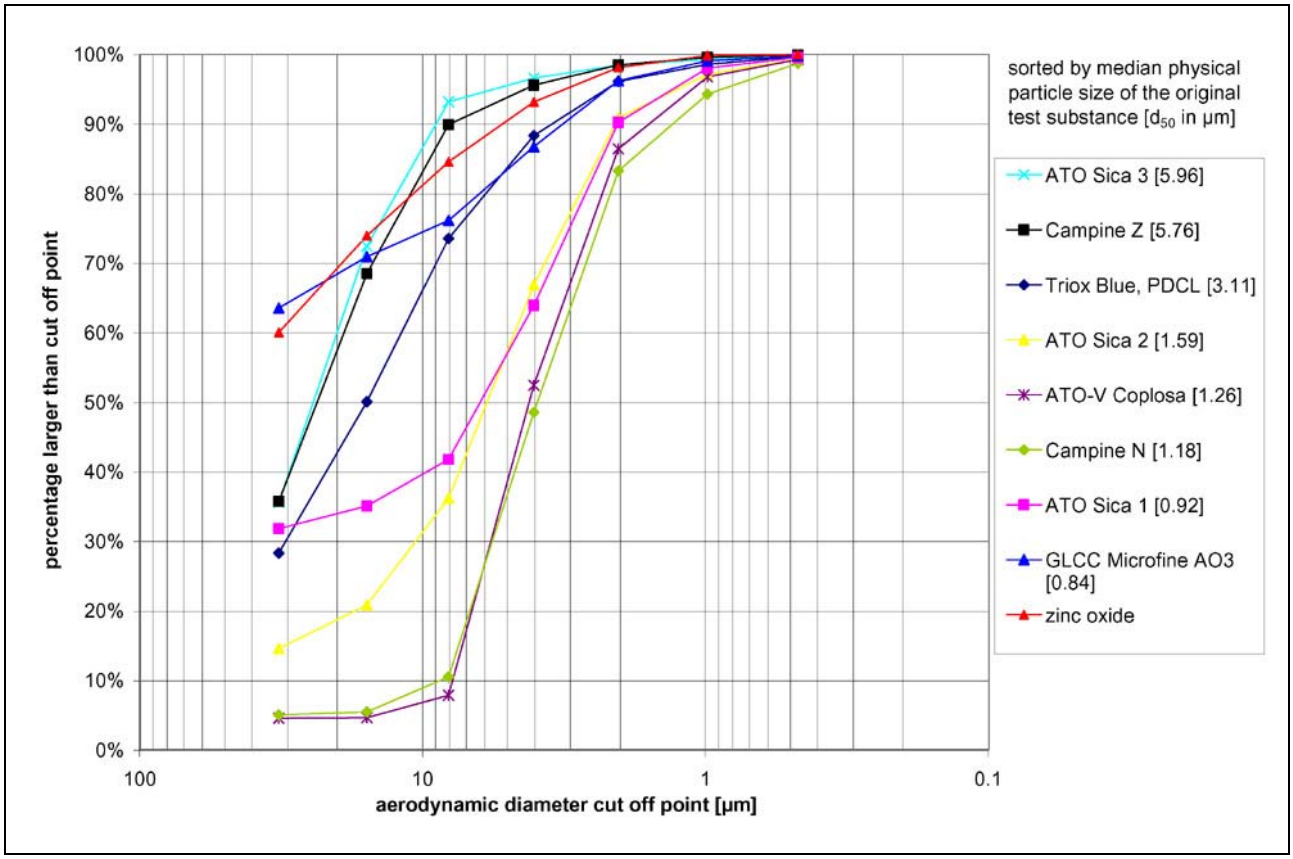


Figure 3: Particle size distribution of the dust that becomes airborne from the samples in the rotating drum according to Heubach

The results presented in graphical form above may initially be interpreted in as follows:

1. The rotating drum method simulates mechanical agitation of dusty solids (such as in bagging, filling and mixing operations) under identical conditions for all samples tested. Therefore, conclusions can be drawn on the likely particle sizes that will be encountered under occupational circumstances when handling the product.

2. Whereas one would expect that the smallest grades of DAT would give the smallest airborne particulates, this is obviously not the case. Instead, the “medium” size range products (physical d50 in the range 1-1.5 µm) obviously generate the finest particle size distribution when suspended in air.

## 5. Summary of results and conclusions

The recently generated data on particle size, dustiness and relative density as presented in the text above (in comparison to zinc oxide) have been summarised in the table below. From the data on particle size distribution of airborne matter obtained during dustiness testing, the MMAD and GSD values were calculated by quasilinear regression by fitting lognormal distributions for each of the substances to its corresponding cascade impactor data based on aerodynamic diameters (in accordance with the procedure set forth in the draft OECD guidance document on acute inhalation toxicity testing: OECD, 2004).

Table 2: Summary of results

| Compound | rel. density[(1)] [g/cm³] | d50[(3)] [µm] | total dustiness[(5)] [mg/g] | MMAD of airborne particles [µm] | Geometric standard deviation (GSD) of MMAD |
|---|---|---|---|---|---|
| ATO Sica 3 | 5.4 – 5.7 | 5.96 | 178.80 | 35.23 | 3.97 |
| Campine Z | 5.44 | 5.76 | 294.42 | 28.85 | 3.53 |
| Triox Blue | 5.6 | 3.11 | 145.48 | 16.87 | 3.58 |
| ATO Sica 2 | 5.4 – 5.7 | 1.59 | 39.81 | 7.42 | 3.03 |
| ATO-V | 5.6 | 1.26 | 18.05 | 4.33 | 2.44 |
| Campine N | 5.44 | 1.18 | 10.91 | 4.12 | 2.64 |
| ATO Sica 1 | 5.4 – 5.7 | 0.92 | 81.49 | 10.21 | 3.49 |
| Microfine®AO3 | 5.5 | 0.84 | 35.97 | 37.01 | 5.00 |
| Zinc oxide | 5.6[(2)] | ~1[(4)] | 30.1[(6)] | 36.04 | 3.70 |

Sources: (1) producer data; (2) Zinc RAR; (3) total particle size analysis (Franke, 2005, 2005a); (4) company data; (5) from dustiness testing (Weidenfeller, 2005, 2005a); (6) from dustiness testing (Armbruster, 2000)

Despite the fact that the use of dustiness and particle size distribution data in the assessment of occupational inhalation exposure is far from standardised, use of these parameters has previously been made successfully in the EU Risk Assessment Reports on Zinc and Zinc compounds for the purpose of extrapolation between compounds. Using the same approach, the following tentative conclusions may be drawn with reference to the possibility of extrapolating from occ. exposure data collected for zinc oxide:

- dermal exposure: the DAT samples of medium and ultra-fine size distribution have total dustiness values of a similar order of magnitude as zinc oxide. It may therefore appear reasonable to extrapolate from zinc oxide to these for the assessment of dermal exposure during handling of finished products. However, since the dustiness of the large particle-size DAT is an order of magnitude higher, extrapolation from zinc oxide could be considered as somewhat limited, and may represent a mild underestimate.
- inhalation exposure: at a first glance, the eight different sample sizes tested apparently show an inconsistent behaviour. However, from this representative range of products in the market, it can be concluded that the material corresponding to the medium particle-size range of products (physical d50 1-15,5 µm) yields the largest proportion of small particles and therefore represents the material with the potentially highest fraction of respirable material, and could therefore be selected as “worst-case” for (i) occupational inhalation exposure assessment, and (ii) for acute inhalation toxicity testing.

## 6. References

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Willeke (1993): K. Willeke. P.A. Baron: Aerosol measurement: principles. techniques and applications. Van Nostrand Reinhold. 1993

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LPT LABORATORY OF PHARMACOLOGY
AND TOXICOLOGY KG

**LPT** Report No. 19226/05

# ACUTE INHALATION TOXICITY STUDY OF ANTIMONY TRIOXIDE IN RATS

**- according to EC Method B.2 (92/69/EC) and OECD Guideline 403 -**

**- Limit Test -**

Sponsor:

**IAOIA**
c/o Mrs. Karine Van de Velde
Campine NV
Nijverheidsstraat 2
2340 Beerse
Belgium

Study conducted by:

**LPT** Laboratory of Pharmacology
and Toxicology KG
Redderweg 8
21147 Hamburg
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Study monitor:

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EBRC Consulting GmbH
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Contact person:

Dr. phil. J. Leuschner

January 24, 2006

This report consists of 58 pages.

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Web-Site: LPT-Pharm-tox.de

## TABLE OF CONTENTS

Page:

## STATEMENT OF COMPLIANCE

## ACUTE INHALATION TOXICITY STUDY OF ANTIMONY TRIOXIDE IN RATS

**- according to EC Method B.2 (92/69/EC) and OECD Guideline 403 -**

**- Limit Test -**

The study was performed in compliance with:

- 'Good Laboratory Practice' Regulations of the EC enacted in Germany in the 'Chemikaliengesetz' [Chemicals Act], current edition;
- United States Food and Drug Administration Good Laboratory Practice Regulations - 21 Code of Federal Regulations, Part 58, current edition.

The following regulations were considered:

- 'OECD Principles of Good Laboratory Practice' Document Nos. 1 and 13 ENV/MC/CHEM (98) 17, ENV/JM/MONO (2002) 9, respectively;
- Japanese Guidelines for Non-clinical Studies of Drugs Manual 1995; Guidelines for Toxicity Studies of Drugs. Japanese Ministry of Health and Welfare.

There were no deviations from the 'Good Laboratory Practice' Regulations. Raw data obtained during the performance of the study are accurately reflected.

This statement covers only the work performed by **LPT**.

Dipl. Biol. F. Chevalier
Study Director

24 Jan 06
Date

## QUALITY ASSURANCE STATEMENT

Based on a quality assurance review, it was concluded that this report accurately reflects the raw data for the study. Methods, procedures and observations are correctly and completely described in the report.

**ACUTE INHALATION TOXICITY STUDY OF**
**ANTIMONY TRIOXIDE**
**IN RATS**
**- according to EC Method B.2 (92/69/EC) and OECD Guideline 403 -**
**- Limit Test -**

Study Plan dated August 19th, 2005 and 1 Study Plan amendment.

| Date of control | Criteria | Date of report to the Study Director and the Management |
|---|---|---|
| 14 Jul 2005 | General inspection of acute inhalation studies in rats: raw data, SOPs, inhalation, filter measurement, filter weighing, surveying and documentation of measurements | 14 Jul 2005 |
| 19 Aug 2005 | Study Plan | 19 Aug 2005 |
| 30 Nov 2005 | SOPs, histotechnique: cutting of microtom, raw data | 30 Nov 2005 |
| 24 Jan 2006 | Final report | 24 Jan 2006 |

In addition, on August 31, 2005 the histology laboratory facilities and procedures at Propath UK Limited were inspected by the QAU of Propath UK Limited and the results were reported on September 01, 2005 to the management of Propath UK Limited.

Approved and submitted by:

F. Hübscher
Director of Quality
Assurance Unit (QAU)
pp Dipl. Biol. O. Hannemann

24. Jan. 2006
Date

## 1. SUMMARY

The aim of the present experiment was to obtain information on the acute toxicity and respiratory irritation, following a single 4-hour exposure of rats to Antimony trioxide in an acute inhalation toxicity study.

Rats were exposed to a dry aerosol of Antimony trioxide at an actual concentration of 5.20 ± 0.16 mg Antimony trioxide/L air for 4 hours by inhalation using a dynamic nose-only exposure chamber. The aerosol was generated with the aid of a dry, rotating brush dust generator.

In the inhalation chamber, close to the animals' noses, the particles had a mass median aerodynamic diameter (MMAD) of 1.664 µm as determined with a cascade impactor. The Geometric Standard Deviation (GSD) of the MMAD was calculated as 4.27. No smaller GSD could be achieved with the test item supplied.

The geometric mean physical diameter of the supplied test item was 0.837 µm as determined with a Malvern Mastersizer.

**Mortality and general signs of toxicity**

Under the present test conditions, a 4-hour exposure to Antimony trioxide at a concentration of 5.20 ± 0.16 mg/L air (analytically verified by gravimetric analysis) caused no mortality, and all animals gained the expected weight throughout the study period.

$LC_{50}$: > 5.20 mg Antimony trioxide/L air

**Clinical signs**

There was a complete absence of any clinical signs of toxicity during the exposure phase, and also during the 14-day post-exposure observation period. In particular, there was also no indication whatsoever of any respiratory irritation, as indicated for example by dyspnoea, rhinitis etc.

**Macroscopic changes in the nasal cavity and lungs**

Multiple red-grey foci (0.1-0.2 mm diameter) in the lung of one satellite animal were noted. No other abnormalities were detected at necropsy.

**Microscopic changes in the nasal cavity and lungs**

A 4-hour exposure to Antimony trioxide at a concentration of 5.20 ± 0.16 mg/L air revealed the following changes:

- The following changes were noted in the lungs (five levels) 24 hours after end of administration:

  All animals revealed an activation of macrophages in the lungs 24 hours after

inhalation of Antimony trioxide. The alveolar lumen contained aggregations of foamy alveolar macrophages and macrophages with phagocytic material (pigment/substance). In addition, inflammatory reactions were noted with granulocytic infiltrations and secretion. Pigment/substance was detected within the secrete and/or mucus. The changes observed are considered to be test item-related but can be explained with physiological clearance mechanisms to be expected after inhalation exposure to such a high concentration of poorly soluble dust material. However, these findings were minimal to mild in severity, and clearly subsided to a large extent after the 14-day observation period.

No test item-related changes were noted in the nose (five levels), larynx and trachea.

- The following changes were noted in the lungs (five levels) 14 days after end of administration:

  All animals revealed an activation of macrophages in the lungs 14 days after inhalation of Antimony trioxide. The alveolar lumen contained only focal aggregations of foamy alveolar macrophages and macrophages with phagocytic material (pigment/substance). In addition, the bronchioli contained mucus with pigment/substance. These findings were minimal to mild in severity and are considered to be test item-related. No inflammatory reactions were noted in the lungs.

  No test item-related changes were noted in the nose (five levels), larynx and trachea.

Hence, histopathology revealed a considerable subsidence of the effects noted in the lungs. The pathological findings after the 14-day observation period improved by decreasing in incidence and severity compared to the findings noted in the animals dissected 24 hours post exposure.

According to the EC-Commission directive 67/548/EC and its subsequent amendments on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances and the results obtained under the present test conditions

**Antimony trioxide**

does not require classification either for

acute inhalation toxicity or for respiratory irritation

Dipl. Biol. F. Chevalier
Study Director

24 Jan 06
Date

## 2. GENERAL INFORMATION

### 2.1 Aim of experiment

the purpose of the study was to obtain information on the acute toxicity, the lowest toxic and lowest lethal concentration ($LC_0$), the $LC_{50}$ and any indication of respiratory irritation following a single 4-hour exposure of rats to the test item in an acute inhalation study. A dynamic inhalation was employed using an open system (nose-only exposure).

### 2.2 Sponsor / Test facility / Responsible personnel

| | |
|---|---|
| Sponsor | **IAOIA**<br>c/o Mrs. Karine Van de Velde<br>Campine NV<br>Nijverheidsstraat 2<br>2340 Beerse<br>Belgium |
| Study monitor | Dr. R. V. Battersby<br>EBRC Consulting GmbH<br>Zeppelinstr. 8<br>30175 Hannover<br>Germany<br>Phone: +49 - 511 - 81 48 32<br>Fax: +49 - 511 - 81 48 78 |
| Test facility | **LPT** Laboratory of Pharmacology<br>and Toxicology KG<br>Redderweg 8<br>21147 Hamburg<br>Germany |
| Study director | Dipl. Biol. F. Chevalier<br>**LPT**, Redderweg 8<br>21147 Hamburg<br>Germany<br>Phone: +49 - 40 - 70 20 20 |
| Deputy study director | Dr. phil. J. Leuschner<br>Phone: +49 - 40 - 70 20 20 |
| Management | Dr. rer. nat. A. Winkler |
| Conduct of study | Dipl. Biol. F. Chevalier |
| Animal husbandry | G. Stehr |
| Veterinarian | Dr. med. vet. G. Rohde |
| Histopathology | Dr. med. vet. M. Wölm |

| | |
|---|---|
| Quality Assurance Unit (QAU) | F. Hübscher |
| Principal Investigator Histotechnique of the nose | I. J. Stiff<br>Propath UK Limited<br>Willow Court, Netherwood Road<br>Hereford, HR2 6JU<br>United Kingdom |
| Test site | Propath UK Limited<br>Willow Court, Netherwood Road<br>Hereford, HR2 6JU<br>United Kingdom |
| Code number of the study in the raw data | 19226/05 |

### 2.3 Rules and regulations

The study was carried out according to:

- EC Method B.2. Acute toxicity (inhalation) (92/69/EEC);
- OECD Guideline for the Testing of Chemicals No. 403: Acute inhalation toxicity, adopted May 12 1981.

In addition, the 'Good Laboratory Practice' Regulations were considered (see the Statement of Compliance and the enclosed GLP Certificate of the Test Facility **LPT**).

| | |
|---|---|
| Standard Operating Procedures (SOPs) | all work was carried out according to standard operating procedures which were followed for all stages of the study; they may be inspected in those divisions which were engaged in the study and in the Quality Assurance Unit (QAU) |
| Staff safety | the standard safety precautions operating within the department were applied to this study |

## 2.4 Archive

| | |
|---|---|
| Archives of raw data and specimens | all specimens, raw data and other documents generated at **LPT** during the course of this study, together with a second print of the final report are stored in the **LPT** archives as required by the 'Chemikaliengesetz' [Chemicals Act]<br><br>**during the study:**<br>in the depot<br>**LPT**, Redderweg 8<br>21147 Hamburg<br>Germany<br><br>**after reporting:**<br>written raw data, specimens and the second print of the final report<br>in Archive 11<br>**LPT**, Redderweg 8<br>21147 Hamburg<br>Germany<br><br>the final report will be archived at the sponsor. |
| Duration of storage | according to the periods laid down in the German 'Chemikaliengesetz' [Chemicals Act]; afterwards the sponsor will decide on further use. |

## 2.5 Study dates

Start of study

| | |
|---|---|
| Date of Study Plan | August 19, 2005 |
| Study Plan amendment | No. 1, dated December 9, 2005 |
| Start of experimental phase | August 26, 2005 |

Study termination

| | |
|---|---|
| Termination of the in-life phase | October 4, 2005 |
| Last date of raw data | December 12, 2005 |
| Date of final report | January 24, 2006 |

## 2.6 Study Plan deviation

The sampling duration was reduced from 20 minutes (as stated in the Study Plan) to 1 minute to avoid overloading of the sampling filter. According to the manufacturer, the sampling capacity of the filter is given as 40 - 50 mg. At the flow rate of 5 L/min and 5 mg antimony trioxide/L, the filter would have been blocked after 2 minutes (50 mg). Therefore, the sampling time was reduced from 20 minutes to 1 minute.

The change does not affect the validity of the study.

# 3. TEST ITEM

## 3.1 Identification of the test item

After receipt at **LPT**, the test item was inspected. Batch number, amount and characteristics (colour, consistency and form) were determined and compared with information given by the sponsor. An identification sheet is then filed with the raw data.

| Test item | Parameter | LPT Identification | Sponsor Identification |
|---|---|---|---|
| **Antimony trioxide** | colour<br>consistency<br>form | white<br>solid<br>powder | white<br>none<br>powder |

No further identification was performed by **LPT**.

## 3.2 Description

| | |
|---|---|
| Designation | Campine N |
| Chemical name | Antimony trioxide |
| CAS no. | 1309-64-4 ($Sb_2O_3$) |
| Batch no. | 29113 |
| Receipt no. | 31327 |
| Date of receipt | June 17, 2005 |
| Characteristics | white powder<br>The geometric mean diameter of the supplied test item was 0.837 $\mu$m as determined with a Malvern Mastersizer (Non-GLP determination). |
| Storage conditions | at room temperature, in a well ventilated dry area, in tightly closed containers |
| Stability | stable until 11/2009 |
| Purity | 99.93%<br>for further information see Appendix 1 'Certificate of Analysis' |
| Retention sample of the test item | stored at<br>**LPT** Laboratory of Pharmacology and Toxicology KG<br>Archive 11<br>Redderweg 8<br>21147 Hamburg<br>Germany |

# 4. METHODS

## 4.1 Animals

| | |
|---|---|
| Species / Strain / stock | rat / CD / Crl: CD(SD) |
| Breeder | Charles River Deutschland GmbH<br>Sandhofer Weg 7<br>97633 Sulzfeld<br>Germany |
| Age<br>(at start of administration) | males: 49 days<br>females: 60 days |
| Body weight<br>(at start of administration) | males: 216 - 230 g<br>female: 201 - 218 g |
| Selection of species | the rat is a commonly used rodent species for such studies |
| Identification of animals | by coloured marks and cage label |
| Number of animals (limit test) | 10 (5 male and 5 female animals)<br>in addition, 3 male and 3 female satellite animals for histopathological examination |
| Group (limit test) | 1 concentration of 5 males and 5 females each; in addition, 3 male and 3 female satellite animals |
| Concentration | 5.20 mg/L air |
| Duration of experiment | at least 5 adaptation days<br>1 test day<br>2 recovery weeks |

**Diet**

ssniff® R/M-H V1534 served as food (ssniff Spezialdiäten GmbH, 59494 Soest, Germany; composition of the diet: see Appendix 2). Feeding was discontinued approx. 16 hours before exposure; only tap water was then available *ad libitum*.

Periodic analysis of the food for contaminants based on EPA/USA[1] is conducted at least twice a year by LUFA-ITL[2] (Limitation for contaminants in the diet: see Appendix 2).

**Housing**

Granulated textured wood (Granulat A2, J. Brandenburg, 49424 Goldenstedt, Germany) was used as bedding material for the cages. The cages were changed and cleaned twice a week.

Periodic analysis of the bedding material for contaminants based on EPA/USA is conducted at least once a year by LUFA-ITL (Limitation for contaminants in the bedding material: see Appendix 2).

During the 14-day observation period the animals are kept by sex in groups of 2 - 3 animals in MAKROLON cages (type III) at a room temperature of 22°C ± 3°C (maximum range) and a relative humidity of 55% ± 15% (maximum range). Deviations from the maximum range caused for example during cleaning procedures are dealt with in SOPs.

The rooms were lit (150 lux at approx. 1.50 m room height) and darkened for periods of 12 hours each.

**Drinking water**

Drinking water in bottles was offered *ad libitum*.

Drinking water is examined according to the 'Deutsche Trinkwasserverordnung 2001' [German Regulations on drinking water 2001] by the Hamburger Wasserwerke, 20539 Hamburg, Germany, at least four times a year (Limitation for contaminants in the drinking water: see Appendix 2).

In addition, drinking water samples taken at **LPT** are analysed by LUFA-ITL once a year for means of bacteriological investigations according to the 'Deutsche Trinkwasser-verordnung 2001, Anlage 1' [German Regulations on drinking water 2001, Addendum 1].

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1 EPA/USA, Proposed Health Effects Test Standards for Toxic Substances Control Act Test Rules, Federal Register 44, 27334 - 27375, May 1979

2 Landwirtschaftliche Untersuchungs- und Forschungsanstalt, Institut für Tiergesundheit und Lebensmittelqualität GmbH, 24116 Kiel, Germany

## 4.2 Administration

| | |
|---|---|
| Route of administration | by inhalation |
| Selection of route of administration | according to possible exposure |
| Duration of exposure to the test item | 4 hours/animal |
| Exposure concentration | 5.20 mg/L air |

## 4.3 Exposure system

The study was carried out using a dynamic inhalation apparatus[3] (air changes/h ($\geq$ 12 times)) with a nose-only exposure of the animals according to KIMMERLE & TEPPER. The apparatus consists of a cylindrical exposure chamber (volume 40 L) which holds a maximum of 20 animals in pyrex tubes at the edge of the chamber in a radial position.

The dust of the test item was generated with a rotating brush dust generator[4].

The generator was fed with compressed air (0.5 bar) from a compressor[4] (air was taken from the surrounding atmosphere of the laboratory room and filtered using an in-line disposable gas-filter).

At the bottom of the exposure chamber, the air was sucked off at a lower flow rate than it was created by the dust generator in order to produce a homogenous distribution and a positive pressure in the exposure chamber (inflow 900 L/h, outflow 800 L/h).

A manometer and an air-flow meter[5] was used to control the constant supply of compressed air and the exhaust, respectively. Flow rates were checked hourly and corrected if necessary.

The oxygen content in the inhalation chamber was 21%. It was determined at the beginning and at the end of the exposure with a DRÄGER Oxygen-analysis test set (DRÄGER Tube Oxygen 67 28 081).

The whole exposure system was mounted in an inhalation facility to protect the laboratory staff from possible hazards.

The exhaust air was sucked through 3 gas wash-bottles filled with tap water. The outlet of the inhalation apparatus was in a DIN certified fume cupboard.

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3 RHEMA-LABORTECHNIK, 65719 Hofheim/Taunus, Germany

4 RBG 1000, PALAS GmbH Partikel und Lasermesstechnik,76229 Karlsruhe, Germany

5 Rotameter, ROTA Apparate- und Maschinenbau, 79664 Wehr/Baden, Germany

Exposition started by locating the rats into the exposure chamber after equilibration of the chamber concentration for at least 15 minutes.

Food was withdrawn approx. 16 hours before the start of the experiment.

| Concentration (mg/L air): | 5.20 |
|---|---|
| Air flow entrance (L/h): | 900 |
| Air flow exit (L/h): | 800 |
| Air change (changes per hour): | 22.5 |

### 4.4 Analysis of the dust

#### 4.4.1 Analysis of the dust concentration

The dust concentration in the inhalation chamber was measured gravimetrically with an air sample filter (Minisart SM 17598 0.45 µm) and pump (Vacuubrand, MZ 2C[6]) controlled by a rotameter. Dust samples were taken once every hour during the exposure. For that purpose, a probe was placed close to the animals' noses and air was sucked through the air sample filter at a constant flow of air of 5 L/min for 1 minute. The filters were weighed before and after sampling (accuracy 0.01 mg). During sampling the air outflow of the exposure chamber was reduced to 500 L/h.

In the report, both the nominal and the actual concentrations are given.

#### 4.4.2 Analysis of the particle size distribution

An analysis of the particle size distribution was carried out twice during the exposure period using a cascade impactor according to MAY[7].

The impactor is a device that classifies particles present in a sample of air or gas into known size ranges. It does this by drawing the air sample through a cascade of progressively finer nozzles. The air jets from this impact on plane sampling surfaces (slides) covered with adhesive tape.

Each stage represents an aerodynamic size range and collects finer particles than its predecessor. Each successive stage represents a special aerodynamic cut off diameter.

The dust from the exposure chamber was sucked through the cascade impactor for 2 minutes at a constant flow rate of 5 L/min. The slides were removed from the impactor and were weighed on an analytical balance (SARTORIUS, type 1601 004,

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6 Membrane Pump,Vacuubrand GmbH + Co., 97877 Wertheim/Main, Germany

7 MAY, K.R. Aerosol impaction jets, J.Aerosol Sci. 6, 403 (1975), RESEARCH ENGINEERS Ltd., London N1 5RD, UK

precision 10 µg).

The correct functioning of the dynamic separation of particles was controlled microscopically during spot-checks.

The mass median aerodynamic diameter (MMAD) was estimated by means of non-linear regression analysis. The 32 µm particle size range and the filter (particle size range < 0.5 µm) were not included in the determination of the MMAD in order not to give undue weight to these values.

The Geometric Standard Deviation (GSD) of the MMAD was calculated from the quotient of the 84.1%- and the 50%-mass fractions, both obtained from the above mentioned non-linear regression analysis.

In addition, a sample of approx. 10 g test item was taken from the exposure chamber to determine the median physical particle size with a Malvern Sizer by Malvern, 71083 Herrenberg, Germany. This determination was non-GLP.

### 4.4.3 Temperature and humidity

Temperature (21.7°C ± 0.6°C) was checked, using a thermometer, and noted once every hour.

The relative humidity amounted to 53.1% ± 3.3%.

## 4.5 Clinical examinations

After completion of exposure, the animals were observed for a period of 14 days.

During and following exposure, observations were made and recorded systematically; individual records were maintained for each animal. A careful clinical examination was made at least once daily until all symptoms subsided, thereafter each working day. Observations on mortality were made at least once daily to minimize loss of animals to the study, e.g. necropsy or refrigeration of those animals found dead and isolation or sacrifice of weak or moribund animals.

Cageside observations included, but were not limited to: changes in the skin and fur, eyes, mucous membranes, respiratory, circulatory, autonomic and central nervous system, as well as somatomotor activity and behaviour pattern.

Particular attention was directed to observation of tremor, convulsions, salivation, diarrhoea, lethargy, sleep and coma. The animals were also observed for possible indications of respiratory irritation such as dyspnoea, rhinitis etc., as specified in more detail in section 4.7.2 of this report.

Individual weights of animals were determined before the exposure and weekly after exposure. Changes in weight were calculated and recorded when survival exceeded one day. At the end of the test, the surviving animals were weighed and sacrificed.

## 4.6 Pathology/Histopathology

**Necropsy**

Necropsy of all main study and satellite animals (5 + 3 males and 5 + 3 females) was carried out and all gross pathological changes were recorded.

**Histopathology**

The main study and satellite animals were subjected to the same level of histopathological examination upon necropsy at the end of the observation period:

- satellite animals: necropsy at 24 hours after cessation of exposure, since this is likely to be the time at which any signs of respiratory irritation would have manifested themselves;
- main study animals: were subjected to the same level of histopathological examination upon necropsy at the end of the 14-day observation period.

The following organs were fixed from all animals in 10% (nose) or 7% (other organs) buffered formalin for histopatholical examination:

- nose (5 levels of the nasal turbinates):

  The tip and Level 1 of the nose were taken from a cut just anterior to the incisor teeth. With tip removed, Level 2 was taken approximately 2 mm posterior to free tip of the incisor teeth. Level 3 was cut through the incisive papilla. Level 4 was cut through the middle of the second palatal ridge which is located just anterior the molar teeth. Level 5 was cut through the middle of the molar teeth. All sections were embedded face down to yield a section from the anterior section, except the nose tip was embedded posterior surface down.
- larynx
- trachea
- lungs (five levels)

Paraffin sections were prepared for all above mentioned organs and stained with haematoxylin-eosin. The preparation of histological slides for the nose were carried out by I. J. Stiff, Propath UK Limited. The slide reading was carried out by **LPT**.

The slides were evaluated by the histopathologist.

## 4.7 Evaluation

### 4.7.1 Statistical procedures

Since no mortality occurred, the calculation of an $LC_{50}$ was not required. Instead, the $LC_{50}$ was assigned to a level equal or greater than the limit concentration tested.

### 4.7.2 Assessment of respiratory tract irritation effects

The Assessment of respiratory tract irritation effects were conducted according to the criteria set forth in the OECD proposal document ENV/JM/HCL(2004)9/REV:

- There are currently no validated animal tests that deal specifically with respiratory tract irritation. However, useful information may be obtained from single and repeated inhalation toxicity tests. For example, animal studies may provide useful information in terms of clinical signs of toxicity (dyspnoea, rhinitis etc) and histopathology (e.g. hyperaemia, oedema, minimal inflammation, and thickened mucous layer) which are reversible and may be reflective of the characteristic clinical symptoms described above. Such animal studies can be used as part of weight of evidence evaluation.
- The special classification would occur only when more severe organ/systemic effects including the respiratory system were not observed.

## 5. LITERATURE

1. OECD Guidelines for Testing of Chemicals, Section 4: Health Effects OECD Publication Office, F-75775 Paris 1981, ISBN 92-64-12-221-4.

2. Offical Journal of the European Communities L 383 A, 29 December 1992.

3. FINNEY, D.J. (1971): "Probit Analysis" Cambridge University Press

4. DIN 66141: Darstellung von Korngrößenverteilungen, DIN 66151: Partikelgrößenanalyse (Beuth-Verlag GmbH, Berlin und Köln)

5. KIMMERLE, G. and A. EBEN: Metabolism, Excretion and Toxicology of Trichloroethylene after Inhalation. 1. Experimental Exposure on Rats. Arch. Toxikol. 30, 115-126 (1973).

## 6. RESULTS

The aim of the present experiment was to obtain information on the acute toxicity and the $LC_{50}$, following a single 4-hour exposure of rats to Antimony trioxide in an acute inhalation toxicity study.

Rats were exposed to a dry aerosol of Antimony trioxide at an actual concentration of 5.20 ± 0.16 mg Antimony trioxide/L air for 4 hours by inhalation using a dynamic nose-only exposure chamber.

### Clinical signs/mortality

Under the present test conditions, a 4-hour exposure to Antimony trioxide at a concentration of 5.20 ± 0.16 mg/L air revealed no clinical signs of toxicity. No mortality occurred.

$LC_{50}$: exceeding 5.20 mg Antimony trioxide/L air

The results are summarized in Table 1, clinical signs in Table 2 and body weights in Table 3.

### Signs of respiratory irritation

There were no signs of respiratory irritation, such as dyspnoea, rhinitis or any other indication of such effects.

### Body weight

All animals gained the expected body weight throughout the study period.

### Dust concentration and particle size distribution

The actual dust concentration of 5.20 ± 0.16 mg Antimony trioxide/L air was measured at the animals nose.

The particle size distribution was analysed using a cascade impactor. The mass median aerodynamic diameter (MMAD) was determined as 1.664 µm at 5.20 mg Antimony trioxide/L air.

The geometric mean diameter of the supplied test item was 0.837 µm as determined with a Malvern Mastersizer.

The results of the analysis of particle size distribution are provided in Table 6 and presented graphically in the Figure 1. Detailed results of the determination of the actual dust concentration are given in Table 7.

The mean actual exposure concentration of Antimony trioxide was as follows:

| nominal concentration | actual concentration | mass median aerodynamic diameter | respirable amount particle size ≤4 µm | |
|---|---|---|---|---|
| [mg/L air] | [mg/L air] | [µm] | [mg/L air] | [%] |
| 11.1 | 5.20 | 1.664 | 2.44 | 47.0 |

The Geometric Standard Deviations (GSD) of the MMAD was calculated as 4.27 at 5.20 mg Antimony trioxide/L air. No smaller GSD could be achieved with the test item supplied

**Pathology/Histopathology**

**Macroscopic changes in the nasal cavity and lungs**

In the satellite animal No. 11 multiple red-grey foci (0.1-0.2 mm diameter) were noted in the lung. No other abnormalities were detected at necropsy.

See Table 4 for detailed results.

**Microscopic changes in the nasal cavity and lungs**

A 4-hour exposure to Antimony trioxide at a concentration of 5.20 ± 0.16 mg/L air revealed the following changes:

- The following changes were noted in the lungs (five levels) 24 hours after end of administration:

  All animals revealed an activation of macrophages in the lungs 24 hours after inhalation of Antimony trioxide. The alveolar lumen contained aggregations of foamy alveolar macrophages and macrophages with phagocytic material (pigment/substance). In addition, inflammatory reactions were noted with granulocytic infiltrations and secretion. Pigment/substance was detected within the secrete and/or mucus. The changes observed are considered to be test item-related but can be explained with physiological clearance mechanisms to be expected after inhalation exposure to such a high concentration of poorly soluble dust material. However, these findings were minimal to mild in severity, and clearly subsided to a large extent after the 14-day observation period.

  Several small haemorrhagic foci are considered to be spontaneous.

  The following changes in the nose (five levels), larynx and trachea were noted:

  Minimal multifocal inflammations (mononuclear or mixed cellular) and epithelial defects of the mucus in some sections of the nose were considered to be related to the technical procedure.

- The following changes were noted in the lungs (five levels) 14 days after end of administration:

  All animals revealed an activation of macrophages in the lungs 14 days after inhalation of Antimony trioxide. The alveolar lumen contained only focal aggregations of foamy alveolar macrophages and macrophages with phagocytic material (pigment/substance). In addition, the bronchioli contained mucus with pigment/substance. These findings were minimal to mild in severity and are considered to be test item-related. No inflammatory reactions were noted in the lungs.

  Several small haemorrhagic foci are considered to be spontaneous.

  The following changes in the nose (five levels), larynx and trachea were noted:

  Minimal multifocal inflammations (mononuclear or mixed cellular) and epithelial defects of the mucus in some sections of the nose are related to the technical procedure.

Hence, histopathology revealed a considerable subsidence of the effects noted in the lungs. The pathological findings after the 14-day observation period improved by decreasing in incidence and severity compared to the findings noted in the animals dissected 24 hours post exposure.

Detailed results of histopathology are given in Table 5

### 6.1 Conclusion

Under the present test conditions, $LC_{50}$-value for rats following inhalation of Antimony trioxide for 4 hours was determined as follows (actual concentration):

$LC_{50}$: > 5.20 Antimony trioxide/L air

Based on the results of the histopathological and macroscopic investigations and the absence of any clinical signs of respiratory irritation, Antimony trioxide does not require classification for respiratory irritation.

According to the EC-Commission directive of September 1st, 1993 on the approximation of the laws, regulations and administrative provision relating to the classification, packaging and labelling of dangerous substances (67/548/EC and its subsequent amendments) and the results obtained under the present test conditions

**Antimony trioxide**

does not require classification either for

acute inhalation toxicity or for respiratory irritation.

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 1 S u m m a r i z e d R e s u l t s

| Symptoms/ Criteria | | 5.20 mg Antimony trioxide/L air males n = 5 | females n = 5 |
|---|---|---|---|
| clinical signs: | | none | none |
| mortality | | | |
| within | 6 h | 0 | 0 |
| within | 24 h | 0 | 0 |
| within | 7 d | 0 | 0 |
| within | 14 d | 0 | 0 |
| mean body weight (in g) (excluding satellite animals) | | | |
| start | | 226.0 ( - ) | 211.4 ( - ) |
| after 7 days | | 295.8 (30.9) | 229.2 (8.4) |
| after 14 days | | 312.4 (38.2) | 235.4 (11.4) |
| inhibition of body weight gain | | none | none |
| necropsy findings | | none | none |

in brackets: body weight gain in % compared to the start value

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 2 Clinical Signs

| Test day | | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8-15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Time after administration | | 0' | 5' | 15' | 30' | 60' | 3h | | | | | | | |
| Animal no./sex | Clinical signs | | | | | | | | | | | | | |
| 5.20 mg Antimony trioxide/L air | | | | | | | | | | | | | | |
| 1 m | none | | | | | | | | | | | | | |
| 2 m | none | | | | | | | | | | | | | |
| 3 m | none | | | | | | | | | | | | | |
| 4 m | none | | | | | | | | | | | | | |
| 5 m | none | | | | | | | | | | | | | |
| 6 f | none | | | | | | | | | | | | | |
| 7 f | none | | | | | | | | | | | | | |
| 8 f | none | | | | | | | | | | | | | |
| 9 f | none | | | | | | | | | | | | | |
| 10 f | none | | | | | | | | | | | | | |

m = male
f = female

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 2 Clinical Signs

| Test day | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 |
|---|---|---|---|---|---|---|---|---|
| Time after administration | 0' | 5' | 15' | 30' | 60' | 3h | 6h | |
| Animal no./sex Clinical signs | | | | | | | | |
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | | | | | | |
| 11 m none | | | | | | | | |
| 12 m none | | | | | | | | |
| 13 m none | | | | | | | | |
| 14 f none | | | | | | | | |
| 15 f none | | | | | | | | |
| 16 f none | | | | | | | | |

m = male
f = female

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 3 Body weight

5.20 mg Antimony trioxide/L air

| Animal no./ sex | TD 0 | TD 8 | | TD 15 | |
|---|---|---|---|---|---|
| | body weight in g | | | | |
| 1 m | 228 | 303 | (32.9) | 321 | (40.8) |
| 2 m | 222 | 297 | (33.8) | 305 | (37.4) |
| 3 m | 224 | 282 | (25.9) | 299 | (33.5) |
| 4 m | 230 | 298 | (29.6) | 315 | (37.0) |
| 5 m | 226 | 299 | (32.3) | 322 | (42.5) |
| Mean | 226.0 | 295.8 | (30.9) | 312.4 | (38.2) |
| SD | 3.2 | 8.0 | | 10.1 | |
| 6 f | 216 | 220 | (1.9) | 222 | (2.8) |
| 7 f | 213 | 237 | (11.3) | 242 | (13.6) |
| 8 f | 209 | 241 | (15.3) | 252 | (20.6) |
| 9 f | 218 | 235 | (7.8) | 245 | (12.4) |
| 10 f | 201 | 213 | (6.0) | 216 | (7.5) |
| Mean | 211.4 | 229.2 | (8.4) | 235.4 | (11.4) |
| SD | 6.7 | 12.0 | | 15.5 | |

TD = test day
TD 0 = Test day 1 immediately before dosing
m = male
f = female
SD = standard deviation
in brackets = body weight gain in % compared to the start value

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 3 Body weight

5.20 mg Antimony trioxide/L air (satellite animals)

| Animal no./ sex | TD 0 | TD 2 | |
|---|---|---|---|
| | body weight in g | | |
| 11 m | 219 | 223 | (1.8) |
| 12 m | 216 | 222 | (2.8) |
| 13 m | 226 | 226 | (0.0) |
| Mean | 220.3 | 223.7 | (1.5) |
| SD | 5.1 | 2.1 | |
| 14 f | 202 | 214 | (5.9) |
| 15 f | 205 | 202 | (-1.5) |
| 16 f | 206 | 205 | (-0.5) |
| Mean | 204.3 | 207.0 | (1.3) |
| SD | 2.1 | 6.2 | |

TD = test day
TD 0 = Test day 1 immediately before dosing
m = male
f = female
SD = standard deviation
in brackets = body weight gain in % compared to the start value

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 4 Macroscopic post mortem findings

| Animal no. and sex | Necropsy findings |
|---|---|
| 5.20 mg Antimony trioxide/L air | |
| 1 m | no pathological findings |
| 2 m | no pathological findings |
| 3 m | no pathological findings |
| 4 m | no pathological findings |
| 5 m | no pathological findings |
| 6 f | no pathological findings |
| 7 f | no pathological findings |
| 8 f | no pathological findings |
| 9 f | no pathological findings |
| 10 f | no pathological findings |

m = male
f = female

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 4 Macroscopic post mortem findings

| Animal no. and sex | | Necropsy findings |
|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | |
| 11 m | lung: | multiple red-grey foci, 0.1-0.2 mm diameter |
| 12 m | | no pathological findings |
| 13 m | | no pathological findings |
| 14 f | | no pathological findings |
| 15 f | | no pathological findings |
| 16 f | | no pathological findings |

m = male
f = female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 1 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 2: | foamy macrophages (multifocal), | mild |
| | | macrophages with pigment/substance, | mild |
| | Level 3: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 5: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus | minimal |
| | Trachea | no pathological findings | |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 2 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | lymphoid hyperplasia, | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 2: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 3: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (focal) | minimal |
| | Level 5: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | mixed cell infiltration (multifocal) | minimal |
| | | mucus (multifocal) | minimal |
| | Level 4: | mixed cell infiltration (multifocal) | minimal |
| | | mononuclear cellular infiltration (focal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 3 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | haemorrhage (focal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 2: | haemorrhage (focal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 3: | haemorrhage (focal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 4: | haemorrhage (focal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 5: | macrophages with pigment/substance | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | mononuclear cellular infiltration (focal), | minimal |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia | mild |
| | Trachea | no pathological findings | |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 4 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 2: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 3: | haemorrhage (focal) | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 4: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 5: | haemorrhage (focal) | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 5 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | haemorrhage (multifocal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mixed cell infiltration (multifocal) | mild |
| | | foamy macrophages (multifocal), | minimal |
| | Level 2: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Level 3: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 5: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | mononuclear cellular infiltration (multifocal), | minimal |
| | | mixed cell infiltration (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | | mixed cell infiltration (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | mixed cell infiltration | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 6 f | Larynx | mucus (multifocal) | minimal |
| | Lungs (five levels) | | |
| | Level 1: | foamy macrophages (focal), | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 2: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Level 3: | macrophages with pigment/substance, | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 5: | lymphoid hyperplasia, | minimal |
| | | foamy macrophages (multifocal), | mild |
| | | macrophages with pigment/substance | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | mononuclear cellular infiltration (multifocal), | minimal |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | | epithelial destruction (multifocal), | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 7 f | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 2: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 3: | macrophages with pigment/substance | mild |
| | Level 4: | macrophages with pigment/substance | mild |
| | Level 5: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | mononuclear cellular infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (focal), | minimal |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 8 f | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | haemorrhage (focal) | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 2: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Level 3: | haemorrhage (focal) | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (focal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 5: | lymphoid hyperplasia, | minimal |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | mixed cell infiltration (multifocal) | minimal |
| | Level 4: | lymphoid hyperplasia, | minimal |
| | | epithelial destruction (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| 9 f | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 2: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | Level 3: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 4: | macrophages with pigment/substance | mild |
| | Level 5: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | mixed cell infiltration (focal), | minimal |
| | Level 2: | mixed cell infiltration (multifocal), | minimal |
| | Level 3: | no pathological findings | |
| | Level 4: | mononuclear cellular infiltration (multifocal) | minimal |
| | Level 5: | mononuclear cellular infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | |
| | Larynx | mononuclear cellular infiltration (focal) | minimal |
| 10 f | Lungs (five levels) | | |
| | Level 1: | macrophages with pigment/substance | mild |
| | Level 2: | lymphoid hyperplasia, | minimal |
| | | foamy macrophages, | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 3: | macrophages with pigment/substance | mild |
| | Level 4: | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance | mild |
| | Level 5: | macrophages with pigment/substance | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | mononuclear cellular infiltration (focal), | minimal |
| | Level 3: | no pathological findings | |
| | Level 4: | mononuclear cellular infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia | minimal |
| | Level 5: | mixed cell infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | mononuclear cellular infiltration (focal) | mild |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 11 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | haemorrhage (multifocal) | minimal |
| | | granulocytic infiltration/secretion | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment | mild |
| | Level 2: | haemorrhage (multifocal) | minimal |
| | | granulocytic infiltration/secretion | mild |
| | | foamy macrophages (multifocal), | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment | mild |
| | Level 3: | haemorrhage (multifocal) | minimal |
| | | granulocytic infiltration/secretion | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | lymphoid hyperplasia, | minimal |
| | | mucus with pigment | mild |
| | Level 4: | haemorrhage (focal) | minimal |
| | | granulocytic infiltration/secretion | mild |
| | | foamy macrophages (multifocal), | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment | mild |
| | Level 5: | granulocytic infiltration/secretion | mild |
| | | foamy macrophages (multifocal), | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | granulocytic infiltration/secretion (focal) | minimal |
| | | mononuclear cellular infiltration (multifocal), | minimal |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Level 5: | mixed cell infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | mononuclear cellular infiltration (focal) | minimal |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 12 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | granulocytic infiltration/secretion | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment | mild |
| | Level 2: | granulocytic infiltration/secretion (multifocal) | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | mild |
| | Level 3: | granulocytic infiltration/secretion (multifocal) | mild |
| | | lymphoid hyperplasia, | minimal |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | mild |
| | Level 4: | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | | granulocytic infiltration/secretion (multifocal), | mild |
| | | lymphoid hyperplasia | minimal |
| | Level 5: | granulocytic infiltration/secretion (multifocal) | mild |
| | | macrophages with pigment/substance, | mild |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | epithelial destruction (multifocal), | minimal |
| | Level 5: | lymphoid hyperplasia, | minimal |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | mononuclear cellular infiltration (focal) | minimal |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 13 m | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment | mild |
| | Level 2: | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Level 3: | granulocytic infiltration/secretion (focal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (locally extensive) | minimal |
| | Level 4: | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Level 5: | granulocytic infiltration/secretion (focal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | minimal |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mixed cell infiltration (multifocal), | minimal |
| | | mononuclear cellular infiltration (multifocal) | minimal |
| | | epithelial destruction (multifocal), | minimal |
| | | mucus (multifocal) | minimal |
| | Level 5: | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | mononuclear cellular infiltration (focal) | minimal |

m male

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 14 f | Larynx | no pathological findings | |
| | Lungs (five levels) | | |
| | Level 1: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 2: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | foamy macrophages (focal), | minimal |
| | | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 3: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 4: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 5: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mixed cell infiltration (multifocal), | minimal |
| | | mononuclear cellular infiltration (multifocal) | minimal |
| | | epithelial destruction (focal), | minimal |
| | Level 5: | mixed cell infiltration, | mild |
| | | lymphoid hyperplasia, | mild |
| | | mononuclear cellular infiltration (multifocal) | minimal |
| | | epithelial destruction (multifocal), | mild |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 15 f | Larynx | mixed cell infiltration (multifocal), | minimal |
| | | epithelial destruction (multifocal), | minimal |
| | Lungs (five levels) | | |
| | Level 1: | haemorrhage (focal) | minimal |
| | | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 2: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 3: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 4: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 5: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mixed cell infiltration (multifocal), | minimal |
| | | mononuclear cellular infiltration (multifocal) | minimal |
| | | epithelial destruction (multifocal), | minimal |
| | Level 5: | mixed cell infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia, | mild |
| | | epithelial destruction (multifocal), | mild |
| | Trachea | no pathological findings | |

f female

TABLE 5 Histopathological findings in microscopic inspections

Microscopic inspections

| Animal No./sex | Affected Organs | Findings | Severity |
|---|---|---|---|
| 5.20 mg Antimony trioxide/L air (satellite animals) | | | |
| 16 f | Larynx | mononuclear cellular infiltration (focal) | minimal |
| | Lungs (five levels) | | |
| | Level 1: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 2: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 3: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 4: | granulocytic infiltration/secretion (multifocal) | minimal |
| | | macrophages with pigment/substance, | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Level 5: | macrophages with pigment/substance | minimal |
| | | mucus with pigment (multifocal) | mild |
| | Nose (5 levels of the nasal turbinates): | | |
| | Level 1: | no pathological findings | |
| | Level 2: | no pathological findings | |
| | Level 3: | no pathological findings | |
| | Level 4: | mixed cell infiltration, | minimal |
| | | mononuclear cellular infiltration (multifocal) | minimal |
| | | lymphoid hyperplasia, | minimal |
| | Level 5: | mixed cell infiltration (multifocal), | minimal |
| | | lymphoid hyperplasia, | minimal |
| | | epithelial destruction (multifocal), | mild |
| | | mucus (multifocal) | minimal |
| | Trachea | no pathological findings | |

f female

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 6 Cumulative particle size distribution

| Particle size [µm] | Filter no. | - Mass fraction [%] - 80 min (after beginning of inhalation) | 160 min | mean |
|---|---|---|---|---|
| 5.20 mg Antimony trioxide/L air | | | | |
| < 0.5 | 0 | 11.8 | 9.8 | 10.8 |
| 0.5 - 1 | 7 | 19.6 | 19.6 | 19.6 |
| 1 - 2 | 6 | 39.2 | 39.2 | 39.2 |
| 2 - 4 | 5 | 47.0 | 47.0 | 47.0 |
| 4 - 8 | 4 | 80.3 | 78.4 | 79.4 |
| 8 - 16 | 3 | 86.2 | 86.2 | 86.2 |
| 16 - 32 | 2 | 94.0 | 92.1 | 93.1 |
| ≥ 32 | 1 | 99.9 | 99.9 | 99.9 |

Acute inhalation toxicity study of
Antimony trioxide
in rats

TABLE 7 Dust concentration

| Time of sampling (in minutes after start of inhalation) | | Actual concentration [mg/L] |
|---|---|---|
| 5.20 mg Antimony trioxide/L air | | |
| 30 | | 5.4 |
| 90 | | 5.0 |
| 150 | | 5.2 |
| 210 | | 5.2 |
| | mean | 5.20 |
| | SD | 0.16 |

SD = Standard deviation

Acute inhalation toxicity study of
Antimony trioxide
in rats

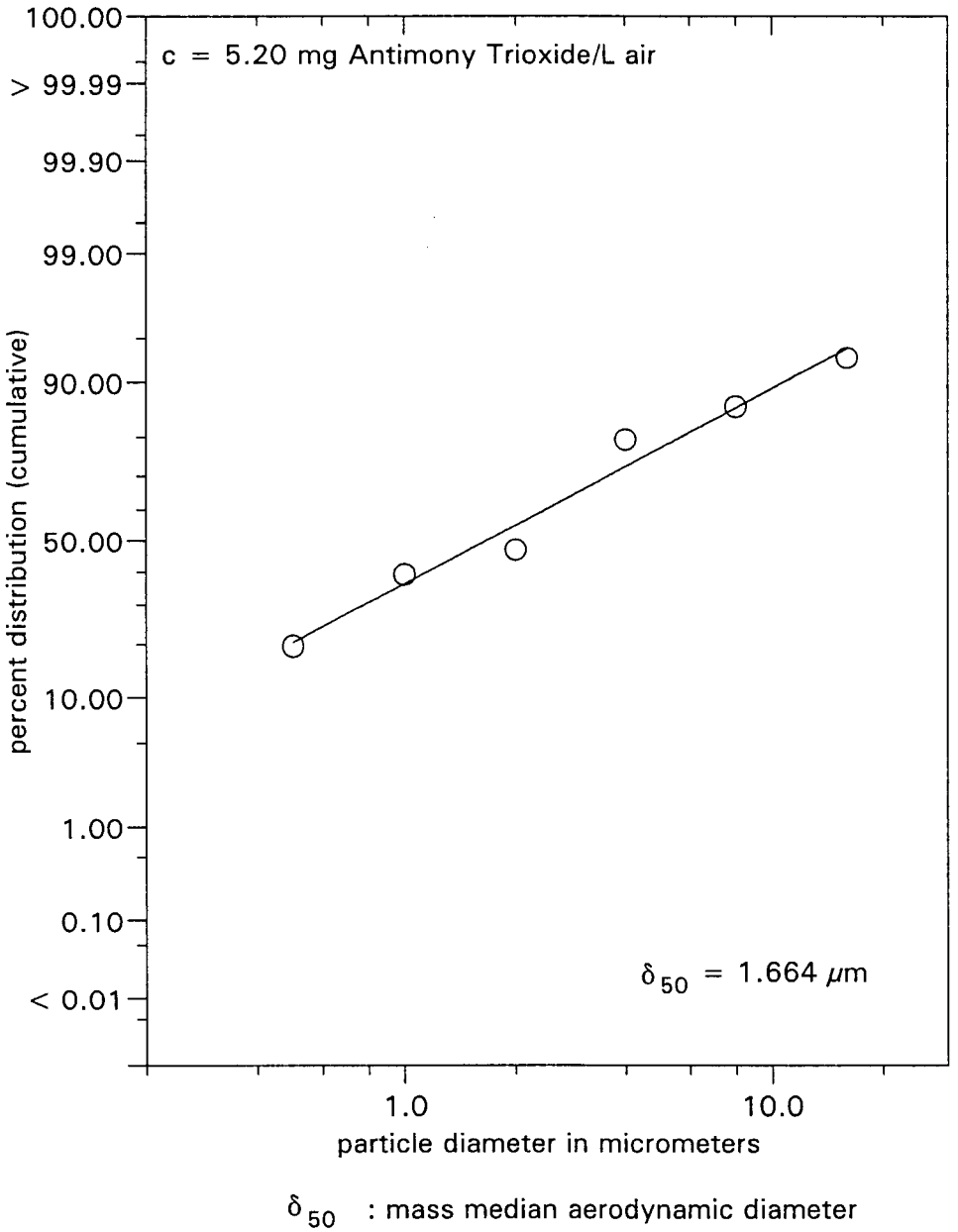
TABLE 8 Temperature and humidity during inhalation

| Time of measuring after start of administration [hours] | Temperature [°C] | Humidity [%] |
|---|---|---|
| | 5.20 mg Antimony trioxide/L air | |
| start | 20.9 | 51.2 |
| 1 | 21.5 | 51.3 |
| 2 | 22.1 | 51.8 |
| 3 | 22.3 | 58.0 |
| mean | 21.7 | 53.1 |
| SD | 0.6 | 3.3 |

SD = Standard deviation

ACUTE INHALATION TOXICITY STUDY
OF ANTIMONY TRIOXIDE IN RATS

Figure 1 particle size distribution
(2 measurements per data point)




$\delta_{50}$ : mass median aerodynamic diameter

# APPENDIX 1

## Certificate of Analysis

# CERTIFICATE OF ANALYSIS

Inspection certificate DIN 50049/3.1.B ( EN 10204/3.1.B)

## CONTRACT INFORMATION

Customer: EBRC
Contract No: 5900399/5210148
Quality: Campine N
Article No: 080101
Batch No: 29113
Weight: 1,1 Kg

## TEST RESULTS

These values have been taken from measurements made on a production run where this batch is a part of.

| Parameter | Unit | Testmethod | Min. | Max. | Actual |
|---|---|---|---|---|---|
| Total Sb2O3 | % | Internal | 99,80 | | 99,93 |
| Pb | ppm | ICP-OES/XRF | 0 | 1000 | 346 |
| As | ppm | ICP-OES/XRF | 0 | 800 | 341 |
| Fe | ppm | ICP-OES/XRF | 0 | 30 | 9 |
| Average particle size | µm | Fisher | 0,80 | 1,00 | 0,91 |
| Sieve refusal 45 µm | % | ISO 787-7 | 0,000 | 0,010 | 0,005 |

We certify that this product conforms to the relevant Campine product specifications: Rev.01/11-09-2003

14/06/2005

F. SMANS

Freddy Smans
quality assurance supervisor

# APPENDIX 2

## Composition of the Diet;
## Limitation for Contaminants in the Diet,
## Drinking Water and Bedding Material

**Composition of the diet**

**Standard Diet for Rats and Mice**
**ssniff® R/M-H V1534**
(ssniff Spezialdiäten GmbH, 59494 Soest, Germany)

| **Ingredients** (average % content in the diet) | |
|---|---|
| crude protein | 19.00 |
| crude fat | 3.30 |
| crude fibres | 4.90 |
| ash | 6.70 |
| **Metabolizable Energy** (MJ/kg) | 12.2 |

| **Amino Acids** (average % content in the diet) | |
|---|---|
| lysine | 1.00 |
| methionine | 0.30 |
| cystine | 0.30 |
| glycine | 0.90 |
| leucine | 1.30 |
| isoleucine | 0.70 |
| arginine | 1.20 |
| phenylalanine | 0.90 |
| tryptophan | 0.25 |
| histidine | 0.50 |
| tyrosine | 0.60 |
| aspartic acid | 1.70 |
| glutamic acid | 3.80 |
| valine | 0.90 |
| threonine | 0.70 |

| **Minerals** (average % content in the diet) | |
|---|---|
| calcium | 1.00 |
| phosphorus | 0.70 |
| sodium | 0.25 |
| magnesium | 0.20 |
| potassium | 0.90 |

| **Trace Elements** (average content in mg per 1 000 g of diet) | |
|---|---|
| manganese | 90 |
| copper | 12 |
| zinc | 75 |
| iodine | 2 |
| iron | 220 |
| selenium | 0.2 |
| cobalt | 2 |

**Vitamins**
(additive per 1 000 g of diet)

| | |
|---|---|
| vitamin A | 15 000 IU |
| vitamin $D_3$ | 1 000 IU |
| vitamin E | 100 mg |
| vitamin $B_1$ | 10 mg |
| vitamin $B_2$ | 20 mg |
| vitamin $B_6$ | 12 mg |
| vitamin $B_{12}$ | 80 µg |
| biotin | 400 µg |
| pantothenic acid | 30 mg |
| choline chloride | 1 600 mg |
| folic acid | 4 mg |
| nicotinic acid | 60 mg |
| vitamin $K_3$ | 5 mg |
| inositol | 50 mg |

**Limitation for contaminants in the diet [ppb]**

| | min. | max. |
|---|---|---|
| Aflatoxin ($B_1$, $B_2$, $G_1$, $G_2$) total | | 5.0 |
| Lindane | | 20.0 |
| Heptachlor | | 20.0 |
| Malathion | | 2 500.0 |
| DDT (Total) | | 100.0 |
| Dieldrin | | 20.0 |
| Cadmium | | 160.0 |
| Arsenic | | 1 000.0 |
| Lead | | 1 500.0 |
| Mercury | | 100.0 |
| Selenium | 100.0 | 600.0 |
| PCB | | 50.0 |

**Limitation for contaminants in the drinking water (mg/L)**

| | max. |
|---|---|
| Iron | 0.2 |
| Manganese | 0.05 |
| Ammonium | 0.5 |
| Chloride | 250 |
| Arsenic | 0.01 |
| Lead | 0.01 |
| Cadmium | 0.005 |
| Chromium | 0.05 |
| Cyanide | 0.05 |
| Fluoride | 1.5 |
| Nickel | 0.02 |
| Nitrite | 0.5 |
| Nitrate | 50 |
| Mercury | 0.001 |
| Vinylchloride | 0.0005 |
| Acrylamide | 0.0001 |
| Benzene | 0.001 |
| Boron | 1 |
| Bromate | 0.01 |
| Selenium | 0.01 |
| Antimony | 0.005 |
| Copper | 2 |
| Aluminium | 0.2 |
| Sodium | 200 |
| Sulphate | 240 |

**Polycyclic aromatic hydrocarbons**

| | |
|---|---|
| - Benzo-(b)-fluoroanthene | |
| - Benzo-(k)-fluoroanthene | |
| - Benzo-(ghi)-perylene | |
| - Indeno-(1,2,3-cd)-pyrene | total 0.0001 |
| - Benzo-(a)-pyrene | 0.00001 |

| | | max. |
|---|---|---|
| **Chlorinated organic compounds** | | |
| Trihalogenemethane including Trichloromethane, Bromodichloromethane, Dibromochloromethane and Tribromomethane | total | 0.05 |
| - 1,2-Dichloroethane | | 0.003 |
| - Tetrachloroethene and Trichloroethene | | 0.01 |
| - Epichlorohydrine | | 0.0001 |
| Organic chemical compounds used as pesticides and biocides including their toxic metabolites | maximum of | 0.0001/substance |
| except for | | |
| - Aldrin | | 0.00003 |
| - Dieldrin | | 0.00003 |
| - Heptachlor | | 0.00003 |
| - Heptachloroepoxide | | 0.00003 |
| | maximum total of | 0.0005 |
| Tritium [Bq/L] | | 100 |
| pH | between | 6.5 and 9.5 |

**Limitation for contaminants in the bedding material (mg/kg)**

| | max. |
|---|---|
| Aflatoxin ($B_1$) | 0.01 |
| Chlordane | 0.05 |
| Endrin | 0.02 |
| Fluorine | 150.00 |
| Lindane | 0.10 |
| Heptachlor and epoxide | 0.03 |
| DDT, DDE, DDD | 0.05 |
| Dieldrin and aldrin | 0.02 |
| Arsenic | 2.00 |
| Lead | 5.00 |
| Mercury | 0.10 |
| Nitrite (Na-Nitrite) | 15.00 |
| HCB | 0.03 |

# APPENDIX 3

## GLP Certificate of the Test Facility LPT

**FREIE UND HANSESTADT HAMBURG**
**Behörde für Wissenschaft und Gesundheit**

# GLP – Bescheinigung / Statement of GLP Compliance

(gemäß/according to § 19b Abs.1 und Anhang 2 des Chemikaliengesetzes
in der Neufassung vom 20. Juni 2002
(BGBl. I S. 2090) in der geltenden Fassung)

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP - Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 88/320/ EG wurde durchgeführt in:

Assessment of conformity with GLP according to Chemikaliengesetz and Directive 88/320/EEC at:

[X] Prüfeinrichtung/Test facility [ ] Prüfstandort/ Test site

Unverwechselbare Bezeichnung und Adresse/Unequivocal name and address:

**LPT Laboratory of Pharmacology and Toxicology KG**
**Redderweg 8**
**21147 Hamburg**
(früher : Praxis Dr. med. Ivo Leuschner/Laboratory of Pharmacology and Toxicology (LPT))

Prüfung nach Kategorien/ Areas of Expertise (gemäß/according ChemVwV-GLP Nr. 5.3/OECD guidance)

**Kategorie 2, 3, 4 und 9 (Sicherheitspharmakologie und Auftragsarchiv)**

Datum der Inspektion/ Date of Inspection:
(Tag.Monat.Jahr/day.month.year)

**23., 24. und 25.11.2004**

Die/Der genannte Prüfeinrichtung /Prüfstandort befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

The above mentioned test facility/test site is included in the national GLP Compliance Programme and is inspected on a regular basis.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung / diesem Prüfstandort die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

Based on the inspection report it can be confirmed, that this test facility/ test site is able to conduct the aforementioned studies in compliance with the Principles of GLP

Hamburg, den 15.4.2005

Behörde für Wissenschaft und Gesundheit 24 Hamburg

Lettau
Amtsleiter

12/22/92

Copy to:
Wm. Rawson
From:
G. Oberdörster
Per your request

# Review of $Sb_2O_3$ Studies

P. E. Morrow and G. Oberdörster

January 1993

## Introduction:

Antimony trioxide, $Sb_2O_3$, (M.W. 291) is a slightly water-soluble, polymorphic crystalline material of industrial importance. Its widespread use in diverse plastics, paper, paint and textile products is based, in large measure, on its special flame retardant properties.

In an early inhalation study conducted in guinea pigs by Dernehl, Nau and Sweets (*J. Industr. Hyg. & Toxicol.* **27**: 256, 1945), antimony trioxide was reported to produce pulmonary irritation, a suppression in granulocytic leukocytes and some fatty infiltration of the liver. In the 1985 edition of the Aldrich Library of Chemical Safety Data, antimony trioxide (Registry of Toxic Effects of Chemical Substances No. CC 5650000) was listed as a Suspected Carcinogen with a Threshold Limit Value (TWA) of 0.5 mg $Sb/m^3$. This information was apparently based on a preliminary report of the results of a chronic study by Watts at the 1980 meeting of the American Industrial Hygiene Society (Sax, 1984). In the most recent ACGIH listing of Threshold Limit Values, the TLV for antimony trioxide (CAS #1309-64-4) remains at 0.5 mg $Sb/m^3$ and is still listed as an A2 Compound (Suspected Human Carcinogen) for exposures during production.

The following review of antimony trioxide studies concerns three important inhalation studies reported during the past decade that were undertaken to provide much needed information on the subchronic and chronic toxicity and carcinogenicity of $Sb_2O_3$.

Watt study:

The thesis by W.D. Watt (1983) gives detailed experimental data on antimony trioxide in CDF female rats (148) and female miniature Sinclair S1 swine (8). Animals were divided into three groups: high and low exposure and control. Exposures to $Sb_2O_3$ used chambers supplied by a dry dust generator (modified hammer mill). The high, 4.2 mg Sb/$m^3$, (5.0 mg/$m^3$ as $Sb_2O_3$) and low, 1.6 mg Sb/$m^3$, exposure groups were delivered the same aerosol with different air dilutions. Rats and swine receiving the same exposure level were exposed in the same chamber.

Watt reported using an SEM for measuring the Feret's diameter on the $Sb_2O_3$ dust. The manner in which the dust was prepared for the SEM is not stated including whether or not the dust was collected as an aerosol or taken from the bulk dust. For the high exposure level, the average particle size was stated to be 0.40 microns with an average GSD of 2.13.

The Watt exposure protocol was for 6 hr/d, 5 d/wk for approximately one year. After 3, 6, and 12 months of exposure the miniature swine were sacrificed under barbiturate anesthesia and pathological and histopathological examinations were performed. The rats were sacrificed and exsanguinated after about 3, 6, 9 and 12 months.

The evaluation in both species during the exposure depended upon serial organ and body weights, hematologic, enzymatic and chemical analyses of the blood, and histopathologic examination of formalin-fixed tissues of major organs by light microscopy. In addition, swine were subjected to X-ray and electrocardiographic examinations before and 6 and 12 months after exposure.

The results of the body weight measurements in rats were confounded by the non-uniformity of group weights at the outset. Both the high and low exposure group rats were significantly heavier than the controls on a pre-exposure basis, but they were

not significantly different at the cessation of exposure. The swine body weight data showed no differences between exposed and control animals.

With organ weights, only the lungs of exposed rats showed significant differences from those of controls. The greater lung weight appeared to correlate with the exposure level and the duration of exposure. Swine lungs showed a similar trend in weight, but the differences from controls were not significant statistically.

Hematologic data included the differential count, RBC count, WBC count, hemoglobin, hematocrit, mean corpuscular volume, and several derived parameters, and these were obtained from both species. No significant differences were found in any of the measurements except for an increase ($p<0.05$) in eosinophils in the high exposure rats at 6 months. Since this increase was not seen at other times, it was probably a chance event.

No changes in serum enzymes and chemistries were found to be significant for the rats or the swine. The investigator points out, however, that the BUN values appeared to rank as high exposure > low exposure > control throughout the exposure of rats. Measurements made included Alk P, SGOT, SGPT, LDH, CPK, BUN, creatinine, bilirubin, $Na^+$, $K^+$, glucose, cholesterol, total protein, and albumin, using commercially-available kits.

Histopathologic examinations were made by several pathologists from Wayne State University, but only Dr. William Busey examined all of the tissues. There were some differences expressed by the pathologists and the examinations were limited to the rats. Dr. Busey concluded that antimony trioxide induced both neoplastic and non-neoplastic tumors in the lungs with a reasonable association with exposure time and level, *e.g.*, the greatest incidence of neoplasia was found in the high exposure group after 90 weeks. Areas of focal fibrosis were seen in rats of the high exposure group as early as 12 weeks of exposure. By the end of the $Sb_2O_3$ exposure, rats in both the

low and high exposure groups exhibited focal pulmonary fibrosis ($p < 0.01$ compared to controls). Adenomatous and pneumocytic hyperplasia, along with cholesterol clefts, were found mainly in the high exposure group. Multinucleated giant cells were significantly greater in the high exposure group rats at 24 weeks and at 52 weeks in the low exposure group.

A random distribution of diverse, extrapulmonary, non-neoplastic alterations was found in the rats, but the pathologists agreed that they were not treatment-related.

Roentgenographic examination of the swine thorax resulted in no abnormalities being detected. The electrocardiographic examinations of swine at pre-exposure, and 6 and 12 months post-exposure, revealed no consistent abnormality. Negative T. waves, normal for miniature swine, showed no consistent change.

The major conclusion drawn from the study was that the findings in female rats do not support the present TLV for antimony. This was the first animal study to show neoplastic changes from $Sb_2O_3$ exposure.

Groth et al. study:

Groth *et al.*, (1986) exposed three groups of Wistar-derived rats (90 males and 90 females each) to either antimony trioxide (45 mg/m$^3$ TWA), Sb ore concentrate (36-40 mg/m$^3$ t.w.a.) or to filtered air for 7 h/d, 5 d/wk, for up to 52 weeks, followed by a 20-week recovery period. In Table 3 of their paper, Groth *et al.*, reported the MMAD (calculated from geometric diameter) of the $Sb_2O_3$ aerosol was 2.80 µm and the MMAD of the ore concentrate aerosol was 4.78 µm. No geometric standard deviations were given. Serial sacrifices were made at 6, 9, and 12 months of exposure and at 18 and 20 weeks after the cessation of exposure. Autopsies and histopathologic examinations were made on all animals.

Lung neoplasia was found in 27% of the females exposed to $Sb_2O_3$, and 25% of the females exposed to ore concentrate. None of the males or control rats developed lung neoplasms.

Arsenic, which usually accompanies antimony, was found in higher concentrations in female tissue than in male tissue. For example, in females exposed to antimony trioxide and to Sb ore concentrate, the blood levels were 230 and 165 μg/g dried blood, respectively. Control female blood levels of As averaged 123 μg/g dried blood. The difference in the As content of $Sb_2O_3$ and of ore concentrate was about 1: 20, but this ratio was clearly absent from the comparative blood levels.

Tissue levels of antimony were highest in the lungs following 9 months of exposure to the trioxide and ore concentrate with 38,000 and 25,600, and 7140 and 4520 μg Sb/g of dried lung found in males and females, respectively. In both cases, the female lungs contained about 65% of the antimony measured in the male counterpart. The wet weight of the rat lungs were stated to be approximately 10 X greater than their dry weight. No lung antimony levels were given at the end of 12 months of exposure, consequently, terminal lung burdens are not known.

Body weight gain in the dust exposed rats was somewhat less than in controls. No difference was found between the survival rates of the exposed and control rats.

After 6 months of exposure, histopathologic examinations of rats from the trioxide exposure revealed septal thickening consistent with interstitial fibrosis, and alveolar wall hypertrophy, hyperplasia and some metaplasia were reported to be prominent in the alveolar ducts. In $Sb_2O_3$ and ore concentrate exposed males at 12 months, there was nearly the same degree of fibrosis as found in the females, but less metaplasia. At the termination of the study at 20 weeks post-exposure, the extent of the interstitial fibrosis had increased in the lungs of both sexes, and neoplasms were found associated with confluent areas of fibrosis in the females only. The female rats

exposed to $Sb_2O_3$ or ore concentrate showed qualitatively similar changes with the degree of fibrosis and metaplasia being comparable.

This study reported an overall 25 to 27% incidence of neoplasms in female rats compared to about 62% incidence in the Watt study conducted at a lower antimony concentration. According to the authors, this could have been due to the fact that the Watt study rats were allowed to live longer. Groth *et al.*, concluded on the basis of their work and others that antimony is both mutagenic and carcinogenic in rats.

**Newton et al. study:**

Newton and Daly (1990) reported a study in which Fischer 344 rats were exposed to $Sb_2O_3$ for one year followed by a recovery period of one year for selected animals. Using $Sb_2O_3$ from 8 suppliers (A-3 Blend) having an average purity of about 99.5%, exposures of Charles River, Kingston, NY, F-344 rats was undertaken at target concentrations of 0.0., 0.05, 0.50, and 5.0 mg antimony trioxide per $m^3$ for 1 year at the rate of 6h/d, 5d/wk. Sixty-five rats of each sex were in each respective exposure group. No special health status was established or maintained on these animals.

The $Sb_2O_3$ aerosol was produced by fluidized bed generators, one model for the lowest exposure level, another for the two higher levels. Particle sizing was done with a TSI Aerodynamic Particle Sizer and a Delron DCI-6 Cascade Impactor.

The most recent description of the Newton *et al.* studies is a paper under review for *Fund. Appl. Toxicology* (1993). In the 2-year oncogenicity study consisting of 12 exposure months and 12 post-exposure months, the mean chamber concentrations of $Sb_2O_3$ were reported to be 0, 0.06, 0.51 and 4.4 $mg/m^3$. The mean particle size of the $Sb_2O_3$ aerosol was reported as having a MMAD of 3.0 µm (GDS 1.6) instead of 3.7 µm reported earlier. Real-time monitoring of the chamber levels was utilized in the chronic study.

At 12, 18 and 24 months into the 2-year study, hematologic samples were taken for standard cytologic and biochemical measurements. Bodyweight measurements were made weekly during the first 13 weeks of the exposure, and monthly thereafter.

Histological examination of hematoxylin-eosin stained tissues in all terminally-sacrificed rats consisted of the heart, nasal turbinates, larynx, trachea, right lung lobes and peribronchial lymph node. Most gastrointestinal, reproductive and endocrine organs were examined grossly and preserved in buffered formalin.

The mean lung concentrations found after 1 year of exposure were 10.6, 120 and 1460 µg Sb/g lung tissue, respectively for the three exposure levels. The aerosol concentration ratios were 1: 10: 90, respectively, while the lung concentration ratios were 1: 11: 138, (males and females combined) respectively, indicating a disproportionate retention in the highest exposure group. The disproportionality is more striking when total lung burdens are compared since the lung concentration data are confounded by a treatment-induced lung weight increase.

At the 5 mg/m$^3$ exposure level, results from a separate 90-day exposure study had given retention halftimes of the deposited $Sb_2O_3$ of 5.6 and 5.3 months for males and females, respectively. These were associated with lung concentrations of about 600 µg Sb/g lung at cessation of exposure and determined over a ~7-month post - exposure period. Retention measurements during the post-exposure phase (12 months) of the 1-year chronic exposure at 0.06, 0.5 and 4.4 mg/m$^3$ $Sb_2O_3$ gave exposure-related halftimes of 2.3, 3.6 and 9.5 months, respectively. These data were summarized in Figure 6 of the Final Report. In Figures F 6-6 and F 6-7 of the Final Report, the post-exposure clearance data are apparently assigned incorrect symbols. According to this report, the 90-day data appear to fit into the relationship between lung burden and retention halftime observed in the one-year exposure groups (See Table 1 of this Review).

In the 1993 manuscript by Newton *et al.*, the pulmonary retention halftimes were described by lung concentration data, not from total lung content and this gives rise to the difference between the retention halftimes given in Table 1 and graphically depicted in the 1993 paper and those provided by the reviewers, as well as certain conclusions drawn from these data.

**Table 1**: Lung burden data and retention halftimes for $Sb_2O_3$ shown in Final Report:

| Exposure duration (months) | Lung burden (µg/g) (both sexes) | Retention halftime (months) |
|---|---|---|
| 12 | 10.6 | 2.3 |
| 12 | 120 | 3.6 |
| 3 | 600 | 5.5 |
| 12 | 1460 | 9.5 |

Pulmonary retention halftimes (by definition, these halftimes indicate when 50% of the initial total lung burden has been eliminated, not a decrease to 50% of the lung concentration) should be calculated based on the retained amount in the total lung (right + left lungs). A comparison of the retention halftimes calculated in this way may indeed indicate a separation between the subchronic and chronic study (see under Critique and Evaluation, Figs. 1-3 and p. 18).

Animals were sacrificed after 6 and 12 months of exposure and at 6 and 12 months of recovery. Postmortem and histopathologic examinations were made on all animals along with special ophthalmic and hematologic evaluations. At the highest exposure level, 4.4 mg $Sb_2O_3/m^3$, dust laden-macrophages, lymphoid aggregates, interstitial inflammation, granulomas, fibrosis and pulmonary adenomatosis were reported to be present in the lungs. No evidence of a pulmonary carcinogenic effect was observed.

Other findings in male rats after one year of exposure included an increase in conjunctivitis (chromodacryorrhea) which was apparently associated with some dental abnormalities. Corneal scars and opacities were found increased in rats of both sexes, but only the opacities were probably treatment-related. The somewhat greater incidence of opacities in the female rats at the 4.4 mg $Sb_2O_3/m^3$ exposure level was more than three times greater than control values. Hematologic evaluations showed an increase in mean corpuscular hemoglobin concentration at the cessation of exposure in both sexes, but not at other times.

No unexpected change was found in body weights among control and exposed groups. Organ weights were likewise unremarkable except for a reported increase in spleen weight at 6-month exposure which was probably unrelated to treatment. The Appendix J data in the Final Report indicate that the control lung weights were consistently less than the lungs from the 4.5 $mg/m^3$ exposure group in both sexes. Only at 18 months in male rats of the high exposure group was the lung weight statistically significant greater than the control, so this may have been by chance. In the Newton *et al.* manuscript submitted to FAAT, it was concluded that the lung weights did not differ between the treatment and control animals nor did the lung/bodyweight ratios change appreciably during the 2-year chronic study.

## Critique and Evaluation

The research by Watt was carried out with ordinary quality animals. The use of swine was potentially very important, but since no histopathologic data were reported for swine, the swine data were used, at best, to document a concern about T wave changes due to antimony that was probably unfounded, but even this documentation is weak, since the swine have a normally peculiar T wave. On a comparative basis with subsequent studies, the Watt study is of poor scientific design and quality. It apparently was never published in a peer-reviewed journal.

The extensive use of blood enzymes and chemistries for both species might have been questioned at the outset, but accepting that a substantial rationale exists for these measurements, they proved to be uniformly negative. This reduced the usefulness of the study to mainly that of providing exposure-related pathologic findings in rat lungs. These findings in female rats were unique at the time. Ideally, the pulmonary pathology should have been related to lung burden of antimony instead of an air concentration. This deficiency is underscored by the differing inhalation study findings of Groth *et al.*, (1986) and Newton *et al.*, (1990, 1993) with antimony trioxide and the reporting of their data in terms of lung burden. Another troublesome feature of the Watt study was the exposure of swine and rats together in the same chamber and the lack of control of bacterial, parasitic and viral infections.

The particle size used in the Watt study was certainly not optimal in terms of dosing the rats pulmonary region. If we assume the particle size reported by Watt was properly obtained based on the Feret's diameter, we can apply the 0.40 μm average size (GSD 2.13) to the Hatch Choate equation (Greene and Lane, 1957) and obtain a MMD of 2.2 μm. Since the average density of $Sb_2O_3$ is 5.5, the MMAD should have been ~5.2 μm (GSD 2.13). It is unlikely that the rat deposited more than a few percent of the aerosol intake. Assuming a rat body weight of 230 g, (average body weight in

the Watt study), a respiratory frequency of 70, a tidal volume of 1.7 $cm^3$, (based on predictive formulas by Stahl, 1967) Schum and Yeh's (1980) model predicts that a rat breathing a 5 $mg/m^3$ aerosol with a 5.2 µm MMAD (GSD 2.13), will deposit 2.0 percent in the tracheobronchial region, 1.85 percent in the pulmonary region and 73.8 percent in the extrathoracic region (naso-pharyngeal region). During a 6-hour exposure, 4 µg Sb will be deposited in the pulmonary region. The retained amount after 1 year, assuming a 70-day retention halftime, and 5 days/week of exposure, would then be ~290 µg. If the retention halftime was prolonged, *e.g.*, 5.5 months (165 days; based on the findings in the study by Newton *et al.*, with comparable lung burdens of $Sb_2O_3$) then the lung burden predicted by the model after 1 year of exposure would be ~530 µg. One has to conclude that a smaller MMAD at the same airborne concentration might have produced greater effects at both exposure levels and provided even more striking evidence of pulmonary toxicity.

The inconsistent evaluations by the several pathologists was a matter not adequately explained. The assumption that Dr. Busey's evaluation should prevail because he alone viewed all of the specimens can be accepted with some reservations. In any case, it is difficult to challenge the two major conclusions derived from the female rat histopathology, *viz.*, that this was the first experimental demonstration of neoplasia with antimony trioxide and that the findings of neoplastic and non-neoplastic pulmonary effects do not support the present TLV for antimony.

The $Sb_2O_3$ and ore concentrate study by Groth and co-workers compared aerosols of the two materials and provided a confirmatory study to that of Watt by finding neoplasia, albeit at a lower incidence rate, in female rats. This is particularly interesting since the rat strain was different (Wistar-derived) and again, no neoplasia was found in males. Findings of non-neoplastic changes, including fibrosis, were also reported for these rats in both sexes.

Groth *et al.*, stated (p. 626) that based on light microscopic examinations of histologic slides from the study of Watt, they deduced that the Watt study rats had less than 10% of the particles in the lungs as they observed in rat lungs from their own study. Considering the smaller particle size (2.8 µm MMAD *vs.* 5.2 µm MMAD) and the higher exposure concentrations (4.2 mg Sb/$m^3$ *vs.* 45 mg Sb/$m^3$), this estimate might be of the right order.

Following an analogous procedure to that used for the Watt study data (p. 10-11 of this review), using standardized respiratory data for the rat from Stahl (1967), the lung deposition model of Schum and Yeh (1980), and the particle size, body weight and 9-month lung burden data from Groth *et al.*, it is possible to estimate the $Sb_2O_3$ and ore concentrate dust pulmonary deposition rates (µg dust/day or µg Sb/day). With this information it can be deduced that the lung burdens at the 9-month timepoint were already at equilibrium and consequently can be used for the 12-month timepoint as well. See Appendix I of this review for more details.

In the Groth *et al.* study, 9 months after the 12-month exposure began, the lung Sb concentrations in males were 38,300 µg Sb/g dried lung and 25,600 µg Sb/g dried lung for the females in the case of antimony trioxide. Assuming the wet weight:dry weight ratio is 10:1, this means the approximate lung concentrations on a wet weight basis were 3,800 and 2,600 µg Sb/g, respectively. Compared to the later study of Newton and Daly conducted for 12 months at a much lower exposure level (4.5 mg/$m^3$ *vs.* 45 mg/$m^3$), the male lung burdens were a factor 3.2 greater while the female burdens were only a factor two greater after 9 months of exposure.

The negative results for neoplasms in males found in the study of Groth *et al.* despite the 46% higher Sb levels in their lungs, possibly point to a remarkable difference in susceptibility among the sexes and greatly complicates the interpretation of these findings in terms of man. It should also be noted that in some studies clearly

involved with dust overloads (Lee *et al.*, 1984; Strom and Garg, 1985; Wolff *et al.*, 1987), there were no important sexual distinctions, *e.g.*, tumor incidence.

The examination of As levels in the Groth *et al.*, study was important. It suggested that the bioavailability of As can be very different, *e.g.*, the trioxide *vs.* the ore concentrate. This interpretation may not be the case because the low levels of As found in all tissues, exclusive of the lungs, is probably evidence of a rapid systemic turnover rate for As in rats (see their Table 6). Moreover, the blood level data revealed only a modest increase in As levels over controls in the face of substantial lung burdens of Sb. Since the pulmonary and extrapulmonary effects of the two materials were comparable in their effects within each sex despite large differences in their As content, it is difficult to incriminate the As content of antimony compounds as responsible for the neoplastic effects seen in the female rats or even to assign it a possible co-factor role.

Since the As content of the $Sb_2O_3$ and antimony ore concentrate aerosols can be determined to be 1.8 μg As/$m^3$ and 30 μg As/$m^3$, respectively, these values can also be incorporated into the 12-month lung burden estimation. Since the retention halftime for As is at least as rapid as that for antimony (Rittmann *et al.*, 1982), the 9 and 12-month As lung burdens should again be comparable.

A recent study reported by Glaser *et al.*, (1982) concluded that they could not demonstrate As to have a significant carcinogenic effect in the rat lungs. Their chronic inhalation study at 60 μg As/$m^3$ and 200 μg As/$m^3$ involved continuous exposure of rats to $As_2O_3$ for 18 months, followed by a 14-month observational period. However, since the Glaser *et al.* study used male rats only, a sex-related difference in susceptibility to As-induced lung tumors could still be postulated.

In the Groth *et al.* study, only a 20-week recovery period followed the one-year of exposure. The fibrosis, hyperplasia and metaplasia reported for the male rats is a

point of special interest, suggesting that studies conducted for longer times might show different results.

The design of the rat study of Newton and co-workers was EPA-approved. It utilized both sexes, a year of exposure and a year of recovery to observe long-term effects, at three different exposure levels besides an air control. It was able to provide both histopathologic data and quantitative information on retained lung burdens. However, no information was given regarding the bacterial, parasitic and viral status of their F344 rats.

The apparent relationship between exposure levels, lung burdens, and retention halftimes which showed a progressive non-linear nature, does not appear to depend upon particulate overloading of the lungs. First, the lower three lung concentrations were generally below the 1 mg dust/g lung level, yet they show a progressive prolongation of retention time. The highest lung concentration appears to exceed the 1 mg/g overload "threshold," but this threshold value is based upon unit density materials. Since $Sb_2O_3$ has a density of about 5.5, the volumetric effect of the 1460 µg/g is only about 300 nl/g, well below the 1000 nl/g value which corresponds to aggregate volume of 1 mg/g of a unit density material (Muhle *et al.*, 1990; Yu *et al.*, 1989; Morrow, 1988).

The non-linearity in retention (see Table, p. 4 of Final Report) is probably due to a mass-related action of antimony trioxide on the lungs. Two recognized explanations for this effect are: (a) clearance by dissolution, *e.g.*, that proposed by Mercer (1965), and/or (b) cytotoxic retardation of clearance, *e.g.*, that reported by Oberdörster (1989) A review of Appendix K information tends to support explanation (b). The Final Report concluded that most of the effects observed, such as inflammatory and fibrotic changes, were most prominent in Group 4, the highest exposure level animals. The absence of histopathologic data at the 600 µg/g lung level (90-day study) and the

order of magnitude difference in lung burdens between the Group 3 and Group 4 rats in the chronic study make this type of conclusion inevitable. The fact that there were even mild chronic toxicity effects seen in the Group 3 animals (at a rather low lung burden of 120 µg/g) is sufficient to relate the retention prolongation to cytotoxic effects rather than citing clearance by dissolution as responsible. To develop the latter argument further, one would need non-equilibrium dissolution measurements on the aerosolized $Sb_2O_3$ and a finding that a solubility model, *e.g.*, Mercer's, predicts the right order of retention halftimes. Even if these were obtained, concern that the cytotoxicity explanation was correct could not be eliminated.

The Appendix K description of tumor incidence and type, and the summary provided in Figure 2 (K26 and 27), support the conclusion made that antimony trioxide did not appear to be oncogenic, a primary conclusion made by Newton *et al.* (1993). The analysis by Dr. William Busey regarding pulmonary neoplasms in the Newton and Daly study and the studies of Watt and Groth *et al.* indicated greater lung burdens of antimony trioxide occurred in the Watt study compared to the Newton and Daly study although the two studies were ostensibly conducted at about the same exposure levels. *Post hoc* measurements of material pigmentation also support this viewpoint and if the assumption of similar retention times is made, an estimate that the Watt study animals had twice their reported lung content of $Sb_2O_3$ was deduced by Newton and Daly.

Assuming the particle size values reported by Watt and the interpretation made of them are both correct, then the dust used by Watt was substantially larger than that used by Newton and Daly. According to the pulmonary deposition estimates of Raabe *et al.* (1978) used in the Yeh model for the F 344 rat, a MMAD of 3.7 µm (Newton and Daly study) should be deposited to the extent of about 5% whilst that of 5.2 µm (Watt study) should be about 1.8% as already discussed. This difference in pulmonary

deposition percentages cannot possibly support a factor two greater deposition in the Watt study as it is diametrically opposite to that position.

In any case, the issue of Watt's study having a factor two greater deposition raised by Newton and Daly, implies that the aerosol concentration used by Watt would have had to be > 20 mg $Sb_2O_3/m^3$ instead of 5 $mg/m^3$. Alternative explanations designed to reconcile the two studies would have to be based on challenging the Watt particle size data on technical grounds or by raising the possibility that the alveolar clearance of $Sb_2O_3$ was substantially less in the Watt study due to a more complete cytotoxic inhibition of the alveolar macrophage system or by invoking the possibility of an unrecognized problem, for example, based on poor hygiene and possible infection(s) in their animals.

Although the study by Newton and Daly did not affirm Groth *et al.* and Watt's finding of antimony-induced neoplasia in the female rats at the highest exposure level, fibrosis and other non-neoplastic changes were found in both sexes. When all is said and done, the difference between a 62% incidence of neoplasms in the female rats of the Watt study and an insignificant incidence of neoplasms in the Newton and Daly study is not satisfactorily explained. Clearly, even a 3 mg/g $Sb_2O_3$ lung level in the Watt study (six times the level predicted based on the reported particle diameter) would not be expected to produce important overloading effects because of the density of 5.5 already discussed and the resulting cumulative particle volume of only ~600 nl/g lung.

Since there were no lung burden data in the Groth *et al.* study except at the 9-month of exposure, there seems to be no basis for comparing retention times or clearance rates with the Newton *et al.* study. Our estimation, however, (p. 12 and Appendix 1 of this Review) indicated a steady state condition probably existed already at 9 months. Consequently, the possibility of lung overloading being an important

component of the study by Groth and co-workers is unlikely. The degree of volumetric overloading was smaller than that believed effective based on many studies (Muhle *et al.*, 1990; Yu *et al.*, 1989), consequently, like in the Newton and Daly study, the maximum expectation from the lung burdens achieved, would, at best, be for a slight reduction in particulate clearance. Undoubtedly, this effect could have some impact on the pathologic course-of-events, but our present understanding of this interplay is not quantifiable. Based on other studies involving dust overload, our judgement is that the interplay would be of inappropriate magnitude to cause the pathology reported. This judgement is supported by the study by Newton and Daly which had similar pathology at lower lung burdens and by the ore concentrate portion of the Groth *et al.* study, where again lower lung burdens yielded comparable pathologic changes in the respective sexes, especially at later times.

On the basis of the manuscript from Newton *et al.*, submitted to Fund. Appl. Toxicol., it appears that nothing of major significance was found at the subchronic 25 $mg/m^3$ level. In fact, the lung concentration data (their Figures 4 and 5) demonstrate a reasonably proportional build up of antimony concentration in both male and female rats relative to all exposure levels used. The clearance data from the subchronic study (Figures 4 and 5) and from the chronic study (Figures 6 and 7 in Newton *et al.* submitted) show again a clearance rate dependence on lung Sb concentration (µg Sb/g lung).

Since lung weights change with age and also due to a cytotoxic effect of the retained compound, it is necessary to express the lung burden as total amount of retained Sb at a given timepoint rather than using the data as µg Sb/g lung for calculation of retention halftimes (see discussion on p. 8 of this Review). Table 2 shows the respective calculated data (not given in the Newton *et al.* manuscript) in

terms of lung burden and retention halftimes, and Figures 1 and 2 of this Review depict the retention data normalized to day 0 (lung burden = 1.0 at end of exposure).

**Table 2**: Retention data of subchronic and chronic $Sb_2O_3$ Exposure Study.

| Exposure Duration Months (m;f) | Exposure Conc. $mg/m^3$ | Lung Burden at Termination of Exposure µg/lung | Pulmonary Retention Halftimes, days |
|---|---|---|---|
| 3 (m) | 0.2 | 41.7 | 54 |
| (f) | 0.2 | 35.4 | 63 |
| (m) | 1.0 | 131.7 | 70 |
| (f) | 1.0 | 128.9 | 73 |
| (m) | 5.0 | 530.3 | 128 |
| (f) | 5.0 | 567.4 | 139 |
| (m) | 25.0 | 1407.4 | 249 |
| (f) | 25.0 | 1926.1 | 279 |
| 12 (m) | 0.05 | 7.8 | 72 |
| (f) | 0.05 | 8.6 | 65 |
| (m) | 0.5 | 84.5 | 85 |
| (f) | 0.5 | 88.4 | 120 |
| (m) | 5.0 | 922.7 | 228 |
| (f) | 5.0 | 1116.1 | 317 |

It appears that the retention halftimes derived from the subchronic and chronic study differ when expressed as a function of the $Sb_2O_3$ lung content at the end of the exposure. The respective data plotted in Figure 3 of this Review suggest that the retention halftimes from the chronic study are longer at equivalent lung antimony levels than those determined for the subchronic study. However, a detailed statistical analysis needs to be performed to support this suggestion.

In terms of dust overloading, it would be logical to expect that a more rapid achievement of the condition of overloading might produce a greater reduction in particle clearance rate, since, in effect, the macrophage clearance function is more apt to be overwhelmed by a high rate of particulate loading. On the contrary, the subchronic data even show less effect on clearance retardation, supporting the viewpoint that the intrinsic toxicity of antimony is responsible for its prolonged retention, and not solely an overloading of the lungs.

Furthermore, Figure 3 of this Review also shows that $Sb_2O_3$ behaves quite differently with respect to the relationship between pulmonary retention halftime and lung burdens compared to particulate material of low intrinsic toxicity such as $TiO_2$. The volumetric burden of the retained dust was found to correlate best with impaired lung clearance when particles of different materials are compared (Morrow, 1988), and a volumetric lung particle burden of ~1 µl in the rat lung was found to indicate the beginning of an overload effect, *i.e.*, the beginning of an increased dust retention halftime. With respect to $Sb_2O_3$ at a density of >5 g/cm$^3$, this would mean that up to a lung burden of about 5000 µg in the rat lung no, or very little, prolongation of clearance should occur. This is clearly not the case as demonstrated by the results of both the subchronic and chronic study (Fig. 3). The build-up of the lung antimony content of the rat lungs in the chronic inhalation study of Newton and Daly, summarized in Appendix M (M-2) of the Final Report, show that the Group II rats of both sex have lower 12-month lung burdens than at 6 months. The build-up curves for the other exposure groups seem almost "flat" during the second-half of the exposure year.

Lung to body weight ratios were higher for rats from the 25 mg Sb/m$^3$ subchronic exposures compared to controls, but only by about 20 percent. Although focal, interstitial inflammation associated with collagen deposition and granulomatous changes were frequently observed at the 25 mg/m$^3$ level and less frequently at the 4.4

$mg/m^3$ chronic exposure level, it is unclear from the statement made on p. 14 and 15 of the Newton *et al.* manuscript (1993) as to what the authors concluded about these changes. Since these pathologic effects were associated with peak lung burdens of about 1-2 mg Sb/g lung tissue (their Figures 4-7), they seem to provide additional evidence for concluding that there is an important intrinsic subchronic and chronic pulmonary toxicity from $Sb_2O_3$ inhalation. In the Abstract of the manuscript of Newton *et al.* (1993), the following statement is made: "Both experimental designs were approved by US EPA. Except for the eyes, no adverse clinical observations were attributed to $Sb_2O_3$ in either study." The operant word is adverse. Perhaps the authors can justify their conclusion based on an accepted definition of adverse. To the reviewers, chronic inflammatory changes, granulomas and fibrosis constitute adverse pulmonary effects.

Newton *et al.* also comment several times in their manuscript about achieving a maximum tolerated exposure level or MTD. For example, in the Abstract (p. 3), they concluded that an MTD was reached due to an 80% reduction in pulmonary dust clearance in the chronic study. The reviewers are aware that some investigators, notably Muhle *et al.* proposed that significantly depressed pulmonary particle clearance in chronic inhalation toxicity studies due to dust particle overload be considered a Maximal Functionally Tolerated Dose or MFTD (Muhle *et al.*, *Fund. Appl. Toxicol.* **17**: 280-299, 1991), but no formal recognition of this proposal has occurred and there are no definitions of MTD which indicate an equivalency to the proposed MFTD. Consequently, the MTD statement by Newton *et al.* is incorrect. .

# Summary and Conclusions

Because of the different experimental methods and designs, *e.g.*, rat strains, exposure levels, and particle sizing, possibly different conditions of animal health, and apparently anomalous findings, *e.g.*, histopathologic and variable lung burdens relative to exposure levels, there is an understandable desire, if not need, to try to reconcile many of these matters so that important similarities and distinctions in the three studies can be accurately portrayed. Our critique is largely devoted to this end. Nevertheless, it is important to concede that we were only partially successful in this pursuit and are highly skeptical that a more complete reconciliation can be achieved. Consequently, we must evaluate the pathologic findings of these studies without the benefit of inter-study consistency.

Our critical assessment of the histopathologic findings compel us to conclude there is ample toxicologic evidence that antimony trioxide ($Sb_2O_3$) dust, and the antimony ore concentrate dust under the test conditions of the Groth *et al.*, study were fibrogenic in the lungs of male and female rats and carcinogenic in the lungs of female rats. Since there was substantial metaplasia and fibrosis found in male rats, longer exposure times could have conceivably led to neoplasia, in fact, this likelihood was suggested by Groth *et al.* While there is a considerable likelihood of confounding factors affecting the outcome of these several studies, such as sex and strain differences and possibly infectivity, on the basis of our current understanding of dust overloading in the rat lung and on the basis of the experimental evidence reported, we do not believe lung overloading , *per se*, can be considered either a causative or confounding etiological factor in the lung pathologic findings of any of the three antimony studies reviewed. On these bases, we further conclude that the pathologic

findings in the rat lungs were most likely induced by the intrinsic toxicological properties of $Sb_2O_3$.

As pointed out in the Introduction of Newton *et al.* manuscript (1993), the EPA deemed the Watt and the Groth *et al.* study designs flawed and their study findings unclear as to the oncogenic potential of inhaled $Sb_2O_3$. This conclusion led subsequently to the EPA-approved studies of Newton *et al.* On the basis of the subchronic and chronic studies undertaken by Newton *et al.*, we concur that no evidence that $Sb_2O_3$ is carcinogenic to the lungs and respiratory tract was found. We feel, however, that a histopathologic examination of all the organs and tissues preserved at sacrifice should have been made. In recent chronic inhalation studjes, increased hyperplasia and tumors were found in non-pulmonary tissues despite little or no evidence for appreciable systemic uptake, *viz.*, adrenal pheochromocytoma in talc-exposed female rats, and forestomach tumors in toner-exposed hamsters (unpublished data). While these findings were clearly treatment-related, they remain controversial and difficult to interpret in human risk assessment. Nonetheless, the decision to limit histopathology on the basis of a gross examination of organs seems unwarranted.

Recently, a NIEHS committee (Lewis *et al.*, 1989) considered the problem of dust overloading and other matters of relevance to chronic inhalation toxicity studies. They recommended that long-term studies be conducted for a minimum of two exposure years. This recommendation was primarily based on findings from several studies in which most of the tumorigenic effects became apparent after 18 months of exposure. This recommendation was also believed appropriate to studies of materials presumed to be of low toxicity in order to maximize the opportunity of detecting any chronic toxicity effects. In any case, the recommendation underscores the importance of time in the development of neoplasia, both with respect to its incidence and severity.

For the recent oncogenicity studies of Newton *et al.*, the EPA-approved design (*circa* 1983) preceded the recommendations of the Lewis *et al.* committee. It is doubtful to the reviewers that the concerns of the NIEHS committee were amply met by a single year of exposure followed by a post-exposure year. Furthermore, the present standard NCI/NTP design for a chronic carcinogenicity study requires a life-long exposure at 3 dose levels in rodents with the highest dose being at the MTD and subsequent lower doses at 1/2 MTD and 1/4 MTD (Haseman, 1985). It is, therefore, unfortunate that this study does not conform to present standards for carcinogenicity testing and thus may not be adequate for classifying $Sb_2O_3$ with respect to carcinogenicity in rats. (See also IARC, 1992).

There is compelling evidence that the increased incidence of pulmonary tumors by dusts of low intrinsic toxicity under the conditions of excessive lung burdens (overload), is a non-genotoxic effect. A recent EPA-sponsored workshop (EPA, 1992) reviewed this general situation and developed possible bases by which this could occur. Nevertheless, the concept is presently unproven and clearly there is no strong circumstantial evidence that this concept could explain the distinction in findings between the recent study of Newton *et al.* and the older studies of Groth *et al.* and Watt. The finding of increased cancer incidence in one rodent sex and not the other is both troublesome and not presently understood. Speculations include gender-based metabolic and endocrine distinctions.

Quite apart from the uncertainties of the oncogenic potential of $Sb_2O_3$, there are consistent findings of toxic pulmonary effects, *e.g.*, fibrosis, from inhaled $Sb_2O_3$ that obligate the reviewers to conclude that $Sb_2O_3$ could not qualify for a "nuisance" dust classification, *viz.*, Particulates Not Otherwise Classified (ACGIH) and Particulates Not Otherwise Regulated (OSHA). Further inhalation studies of antimony designed according to present standards are indicated. Although costly and time-consuming,

such studies are needed because the available toxicological data base is seriously limited and hampered by important gaps and inconsistencies in the study designs and experimental findings to date.

Respectfully submitted,

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# Relative Lung Retention after Antimony Trioxide Exposure Male Rats

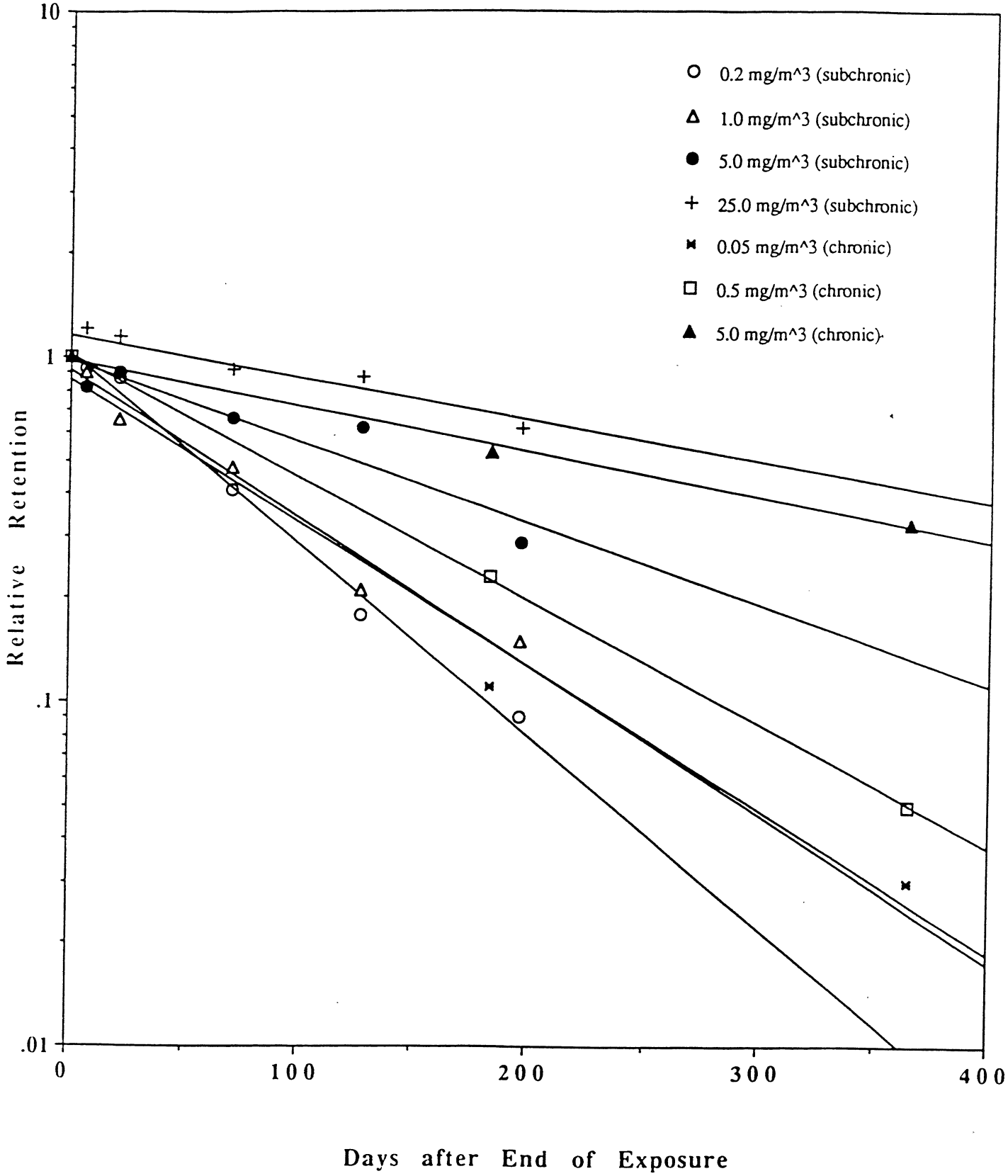



FIG. 1

# Relative Lung Retention after Antimony Trioxide Exposure Female Rats

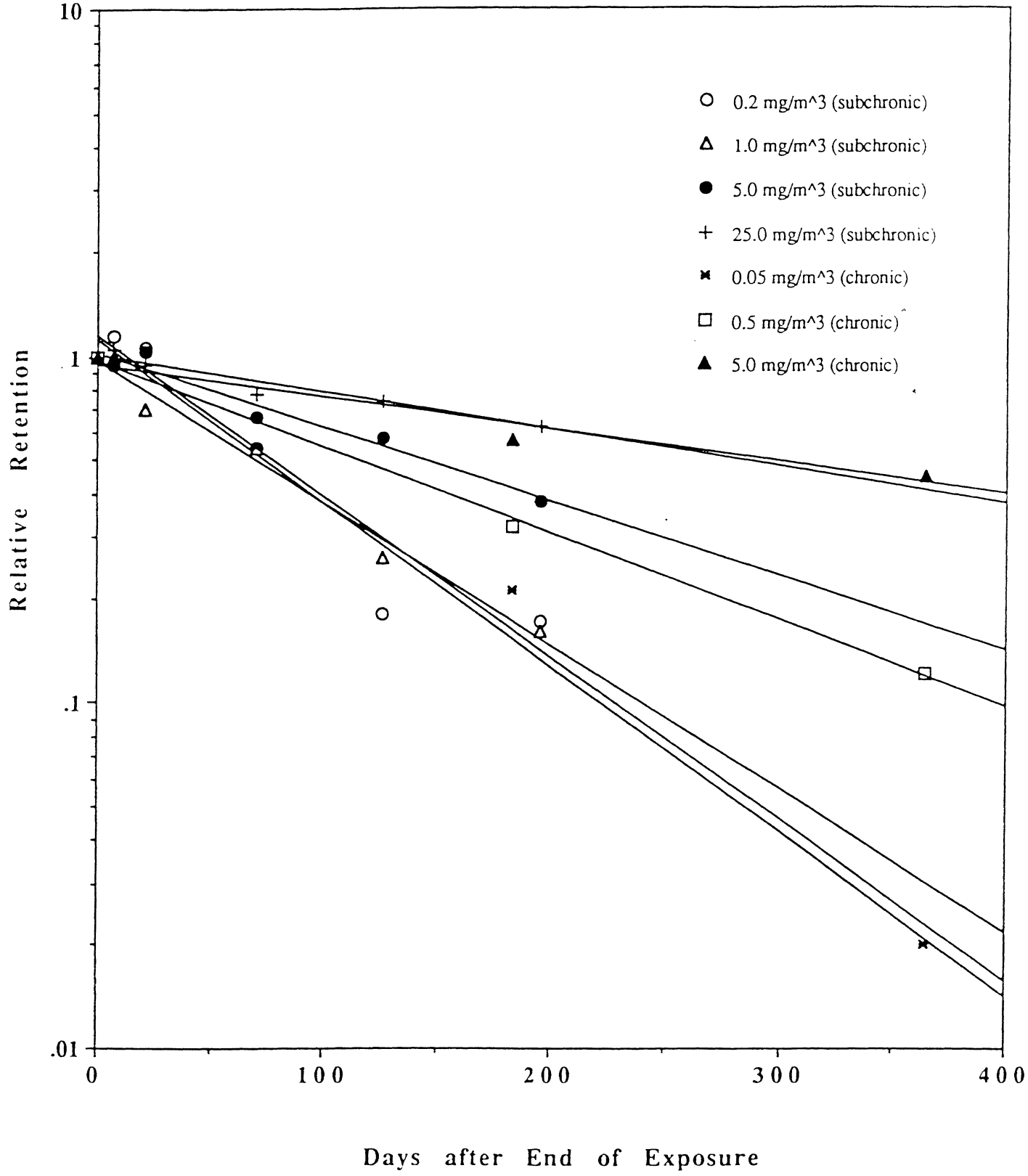
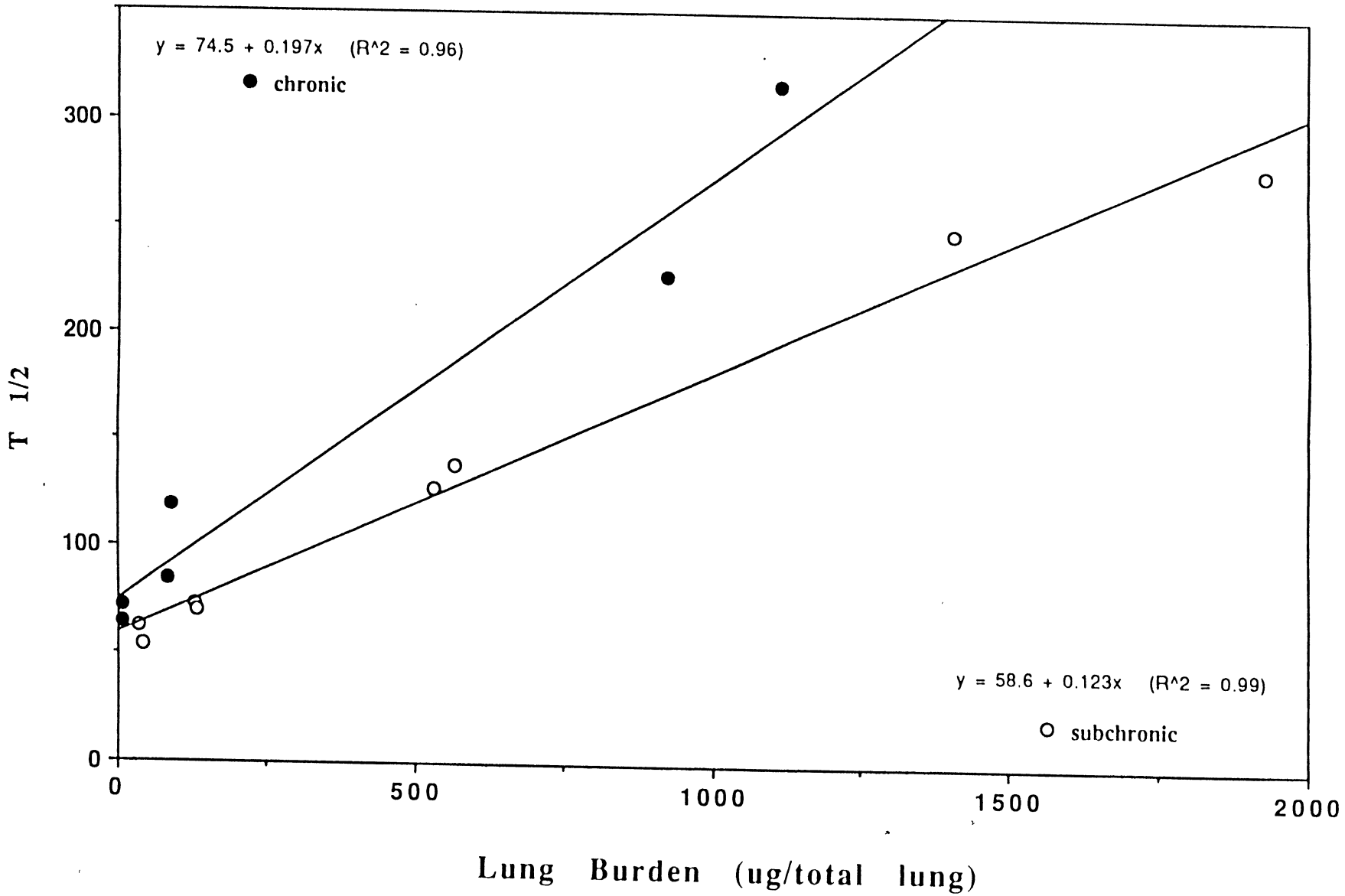



FIG. 2

## Pulmonary Antimony Trioxide Levels at End of Exposure and Retention Half-times, T 1/2



## LIST OF ACRONYMS

| | |
|---|---|
| ACGIH | American Conference of Governmental Industrial Hygienists |
| Akl P | Alkaline Phosphatase |
| BUN | Blood Urea Nitrogen |
| CDF | A specific strain notation of rats used by Watt |
| CPK | Creatine Phosphokinase |
| FAAT | Fundamental and Applied Toxicology |
| GSD | Geometric Standard Deviation |
| IARC | International Agency for Research on Cancer |
| LDH | Lactic Dehydrogenase |
| MMAD | Mass Median Aerodynamic Diameter |
| MTD | Maximum Tolerated Dose |
| NCI | National Cancer Institute |
| NIEHS | National Institute of Environmental Health Science |
| NTP | National Toxicology Program |
| RBC | Red Blood Cell |
| SEM | Scanning Electron Microscope |
| SGOT | Serum Glutamic Oxylacetate Transaminase |
| SGPT | Serum Glutamic Pyruvate Transaminase |
| TLV | Threshold Limit Value |
| TWA | Time Weighted Average |
| WBC | White Blood Cell |

# APPENDIX I

Adjustment of Sb lung burdens reported in the Groth *et al.* study after 9 months of exposure to a 12-month exposure duration.

To provide AOIA a clearer view of the justification for using the 9-month lung burdens reported by Groth *et al.* in their study we include the following material which summarizes the various parameters required and provides computations based on the lung model by Schum and Yeh (1980).

The lung burdens reached at 9 months were as follows for the different groups:

**Table I**

9-month lung burdens in Groth *et al.* study (mg Sb/g wet weight)

| | $Sb_2O_3$ | Sb-ore |
|---|---|---|
| Males | 3.83 | 0.71 |
| Females | 2.56 | 0.45 |

For computing the deposited doses of the inhaled dusts, average body weights reported by Groth *et al.* were used to predict tidal volumes, respiratory rates and lung weights based on Stahl (1967). Resulting values are tabulated below:

**Table 2**

Respiratory parameters for rats in Groth *et al.* study

| | | Males | Females |
|---|---|---|---|
| $Sb_2O_3$ | Body weight, g | 585 | 390 |
| | Tidal volume, ml | 4.4 | 2.9 |
| | Resp. rate, $min^{-1}$ | 56 | 61 |
| | Lung weight, g | 6.7 | 4.4 |
| Sb-ore | Body weight | 615 | 380 |
| | Tidal volume, ml | 4.6 | 2.8 |
| | Resp. rate, min-1 | 56 | 62 |
| | Lung weight, g | 6.8 | 4.4 |

For prediction of the daily deposited amount with the deposition model of Schum and Yeh (1980), the above respiratory parameters and the mass median aerodynamic diameter (MMAD) of the inhaled particles given by Groth *et al.* ($Sb_2O_3$: 2.8 μm; Sb-ore: 4.78 μm) were used as input values in the computer model. Since no geometric standard deviation (GSD) was provided in the published paper, an assumed value of 1.8 was used. With these input values and the given concentrations of 45 mg/m$^3$ for $Sb_2O_3$ and ~38 mg/m$^3$ Sb-ore, the following daily deposited doses (7 h exposure) were computed:

**Table 3**

Daily (7 hr. exposure) deposited doses of inhaled Sb-compounds in pulmonary region in rats of Groth et al. study for chronic exposure, adjusted for 5 days per week exposure (μg)

| Deposited as | $Sb_2O_3$ | Sb | Sb-ore | Sb |
|---|---|---|---|---|
| Males | 756 | 605 | 402 | 185 |
| Females | 368 | 295 | 184 | 84 |

If one assumes that the clearance of the inhaled dust was retarded due to either a toxic effect on alveolar macrophages or an "overload" related effect one would calculate with the above daily deposition values a total lung dust burden much higher than reported by Groth *et al.* On the other hand, assuming a retention halftime of 30 days for $Sb_2O_3$ and a very short halftime of 18 days for Sb-ore would very well predict the reported values for a 9-month exposure, as shown in the following table:

## Table 4

Accumulated lung burden (A) at 9 months of exposure according to:

$$A = \frac{a}{b} \cdot (1 - e^{-bt})$$

A = accumulated lung burden (mg); a = daily deposited amount, mg;

b = clearance rate = $\frac{\ln 2}{T\ 1/2}$; t = exposure time in days

| | $Sb_2O_3$ | | Sb-ore | |
|---|---|---|---|---|
| | Sb (total lung,mg) | Sb (mg/g) | Sb (total lung, mg) | Sb (mg/g) |
| Males | 26.2 | 3.91 | 4.8 | 0.71 |
| Females | 12.8 | 2.9 | 2.2 | 0.50 |

---

A comparison with Table 1 shows the good agreement of the predicted with the observed values. The problem, obviously, is that we had to apply very short retention halftimes to compute these values. These short retention halftimes are not in good agreement with the findings of Newton and Daly; however, applying longer retention halftimes would have resulted in much higher lung burdens than actually found by Groth *et al* as pointed out above.

Since the model predictions of deposition are based on actual data found in particle deposition studies by Raabe *et al.* (1978; 1988) which are verified in numerous other studies as well and since short retention halftimes of 18 and 30 days are highly unlikely for these Sb-compounds, our assumptions for the input values of the deposition model are likely to be wrong. These assumptions on particle size parameters (MMAD and GSD) are based on the sketchy information given in the Groth *et al.* study and there is no way to improve on that without getting additional details from Groth *et al.*

The lung weight of the rats in the Groth *et al.* study computed by Stahl's formula (Table 2) are rather high, and one might use other predictions which would give a lower value. However, doing so would lead to a higher than observed Sb lung concentration predicted by the model, unless even shorter retention halftimes were assumed. Thus, based on the inadequate information provided in the Groth *et al.* study, the only conclusion we can draw, with regard to lung burdens, is that at 9 months of exposure steady state conditions were reached in the lungs of their rats and that consequently these reported 9-month values should be used for the 12-month timepoint as well. This conclusion is also consistent with the result of the Newton *et al.* study in which the lung burdens of $Sb_2O_3$ were found to have nearly plateaued between 6 and 12 months of exposure.

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TNO report

V6502

# A study on the Biodistribution of Antimony trioxide ($Sb_2O_3$) in rats

| | |
|---|---|
| Date | 12 December 2005 |
| Status | Final |
| Authors | A.Th..J deBie<br>Dr. F.G.C. Salmon-te Rietstap |
| Sponsor | International Antimony Oxide Industry Association<br>c/o Karine Van de Velde<br>IAOIA Secretary-General<br>Nijverheidsstraat 2<br>2340 Beerse<br>Belgium |
| TNO project number | 31524 |
| TNO study code | 6502 |
| Study monitor | K. van de Velde |
| Status | Final |
| Previous versions | Draf1, 11 November 2005<br>Draft 2, 30 November 2005 |
| Number of pages | 63 |

# GLP compliance statement

I, the undersigned, hereby declare that this report constitutes a complete, true and accurate representation of the study and its results. All study activities performed by TNO Quality of Life were carried out in compliance with the current OECD Principles of Good Laboratory Practice (Organisation for Economic Co-operation and Development, Paris, ENV/MC/CHEM (98) 17). Characterisation and verification of the identity and properties of the study substances were, however, the responsibility of the sponsor.

A.Th.H.J. de Bie
(Study director) _____ Date

---

Approved by:

Dr. Ir. A.F.M. Kardinaal
(Management, Physiological Sciences) _____ Date

# Quality assurance statement

On: A study on the biodistribution of Antimony trioxide ($Sb_2O_3$) in rats
Report Number: V6502
Date : 12 December 2005

*The study plan was audited as follows:*

| Date of inspection: | Date of report: |
|---|---|
| 14 July 2005 | 14 July 2005 |
| 1 August (Amendment I) | 1 August 2005 |

*The experimental phase was audited as follows:*

| Date of inspection: | | Date of report: |
|---|---|---|
| 19 July 2005 | Preparation of dose solution and dose administration | 19 July 2005 |
| 26 July 2005 | Preparation of dose solution, dose administration and blood sampling | 26 July 2005 |
| 29 July 2005 | Collection of organs/tissues | 29 July 2005 |
| 1 August 2005 | Sample preparation and coding | 1 August 2005 |
| 2 August 2005 | Sample filtration and registration for ICP-AES | 2 August 2005 |

*This report was audited as follows:*

| Date of audit: | | Date of report: |
|---|---|---|
| 9 December 2005 | Draft report and dossier | 11 December 2005 |
| 12 December 2005 | Final report | 12 December 2005 |

I, the undersigned, hereby declare that this report provides an accurate record of the procedures employed and the results obtained in this study; all audits were reported to the study director and the management on the dates indicated.

P.B. Davis
(Quality Assurance Auditor)

_____
Date

# Table of contents

# Abbreviations

| | |
|---|---|
| BW | body weight |
| GI | gastro-intestinal |
| ICP-AES | inductively coupled plasma-atomic emission spectrometry |
| ICP-MS | inductively coupled plasma-mass spectrometry |
| IP | intraperitoneal |
| IV | intravenous |
| LOD | lower limit of determination |
| PO | oral |
| Sb | antimony |
| $Sb_2O_3$ | antimony trioxide |

# Summary

The present study was conducted in order to estimate the oral bioavailability of antimony trioxide ($Sb_2O_3$) and determine the rate and route of excretion of $Sb_2O_3$ after oral (PO), intravenous (IV) or intraperitoneal (IP) dosing in the rat. The study was also designed to contrast absorption kinetics and the ability to reach bone marrow after acute PO and IP exposure and to determine the pattern of tissue distribution and excretion following acute and repeated PO exposure.

The study comprised the following six groups of rats:

| Group | Route | Dosing frequency | Dose level | In-life period | Number of |
|---|---|---|---|---|---|
| A | IV | single | 1.57 mg/kg $SbCl_3$ | 3 days | 4♂ |
| B | IP | single | 100 mg/kg $Sb_2O_3$ | 3 days | 4♂ |
| C | PO | single | 100 mg/kg $Sb_2O_3$ | 3 days | 4♂ + 4♀ |
| D | PO | single | 1000 mg/kg $Sb_2O_3$ | 3 days | 4♂ + 4♀ |
| E | PO | 14 day repeated | 1000 mg/kg $Sb_2O_3$ | 14 + 3 days | 4♂ + 4♀ |
| F | Control | non-dosed (background) | | 1 day | 4♂ + 4♀ |

No study- or test substance-related signs of toxicity or unusual behaviour were observed. Body weight gain was normal.

Blood, plasma, urine, faeces and several organs (bone marrow, liver, brain, femur, kidneys, thyroid, lungs, testes, uterus, muscle, heart, prostate, ovaries, skin, spleen), residual carcass and gastro-intestinal (GI)-tract including content were collected for analysis of the antimony concentration by ICP-AES (faeces and dose formulations) or by ICP-MS (blood, urine, cage wash and tissue), both after sample destruction with aqua regia.

*Blood kinetics*
The blood concentration of antimony (Sb) versus time curve after intravenous injection for group A showed a rapid distribution phase from the blood into an extravascular compartment. The lowest blood concentration of Sb was reached 4 hours after injection. From this time point on, Sb was redistributed to blood and showed a concentration versus time curve very similar to the curves observed after oral administration of $Sb_2O_3$ at both the single oral low and high dose (groups C and D) with an absorption phase and an elimination phase. After oral administration, the absorption from the GI-tract into the vascular system was slow with a $C_{max}$ at approximately 24 hours after dosing. The absorption from the dosing site was determined to be not complete in the IP-dosed animals (Group B). The data generated from this group are therefore difficult to interpret and are considered unreliable. No accurate half-life could be calculated from the obtained kinetics curves. However, a bioavailability factor could be calculated from the AUC ($_{0\text{-}72h}$) of the intravenous and oral groups, which showed that the oral bioavailability of Sb is low but significant in both the single oral low dose (C) and the single oral high dose (D) groups with values of 0.3% and 0.05%, respectively.

It was concluded that the absorption of Sb from the GI- tract was a slow and saturable process.

*Absorption and excretion*
After an intravenous dose (group A), around 30% of the total Sb was excreted in the faeces within the first 24h and around 14% was recovered in the urine 72h after dosing. In the IP-dosed animals (group B), 36% of the Sb was recovered from the faeces whereas in the orally dosed animals around 80% and 100% of the dosed Sb was excreted via the faeces 72h after dosing for the single low and the single high dose group, respectively. Only very low amounts of antimony were found in the urine, the tissues and carcass in both the orally dosed groups. These results correlate with the oral bioavailability of around 0.3% and 0.05% calculated from the blood concentration curves for the low and the high dose group, respectively.

Both the recovery of Sb in urine and tissues and the calculated bioavailability are approximately 5 to 7 times lower for the oral high dose (group D) than for the oral low dose (Group C) confirming that the oral absorption is a saturable process.

*Tissue distribution*
The Sb concentration in bone marrow seemed to correlate with the whole blood concentration in both the intravenous and the oral low dose group. The ability of Sb to reach bone marrow after a single oral low dose in rats was around ten times lower than in the intravenously dosed rats. In the IP-dosed animals, however, the Sb content in bone marrow was approximately four times higher than the blood concentration in these animals and approximately forty times higher than in the bone marrow of the oral low dose rats. The Sb concentration in the bone marrow of the control group was higher than the Sb concentration in other tissues and, thus, similar to the concentration in the bone marrow of the oral low dose group. In the oral high dose group the Sb concentration in bone marrow was much higher than in whole blood indicating that appreciable amounts of antimony were distributed to bone marrow. After repeated oral high dosing the Sb concentration in bone marrow increased less than the concentration in whole blood, which was not the case in the single oral high dose group. This result could indicate a saturation of the bone marrow tissue after repeated dosing.

A similar pattern was seen for the thyroid where the Sb concentration after the single oral low dose was comparable to the control, increased about ten times after a single oral high dose but did not increase significantly after repeated oral high dosing. It is noticeable that in control animals the Sb concentration in the thyroid was as high as in the bone marrow and much higher than in whole blood.

In most of the other studied organs the Sb concentration increased moderately either after a single oral low or a single oral high dose. After repeated oral dosing, Sb content was increased in all organs, but not in proportion to the increase in dose.

*Conclusions*
It can be concluded that the absorption of Sb after oral dosing of $Sb_2O_3$ is a slow and saturable process. Sb is poorly absorbed, but undergoes significant distribution as it binds to red blood cells. Appreciable amounts are distributed to bone marrow via all routes of dosing. It can also be concluded that $Sb_2O_3$ undergoes urinary and biliary excretion after oral dosing.

# 1 General

## 1.1 Study sponsor and monitor

| | |
|---|---|
| Sponsor | International Antimony Oxide Industry Association<br>c/o Karine Van de Velde<br>IAOIA Secretary-General<br>Nijverheidsstraat 2<br>2340 Beerse<br>Belgium |
| Study monitor | K. van de Velde |
| Email address | karine.vandevelde@campine.be |

## 1.2 Testing facility

TNO Quality of Life, Business Units Physiological Sciences, Toxicology and Pharmacology, and Analytical Services

| | |
|---|---|
| Postal address | P.O. Box 360, 3700 AJ Zeist, The Netherlands. |
| Location | Utrechtseweg 48, 3704 HE Zeist, The Netherlands. |
| Telephone | +31 30 694 4144 |
| Fax | +31 30 6944986 |

## 1.3 Responsible personnel

| | |
|---|---|
| Study director | A.Th.H.J. de Bie[1]<br>E-mail: debie@voeding.tno.nl |
| Deputy Study Director | Dr A.P. Freidig[1] |
| Animal care | G. van Beek[2] |
| Antimony analysis | H.P.M. de Haan[3] |
| Management | Dr A.F.M. Kardinaal[1] |

[1] Business Unit Physiological Sciences
[2] Business Unit Toxicology and Pharmacology
[3] Business Unit Analytical Services

## 1.4 Time schedule experimental phase

The experimental phase of the study was conducted at the testing facility from 13 July 2005 (arrival of the animals) to 29 November 2005 (last analysis of samples) according to study plan P6502 entitled “A study on the biodistribution of Antimony trioxide ($Sb_2O_3$) in rats”, approved by the Study Director on 4 July 2005, and amendment I to this plan approved on 14 July 2005.

# 2 Introduction

## 2.1 Objective

The present study was conducted in order to:

- estimate the oral bioavailability of antimony trioxide ($Sb_2O_3$) at two different dose levels in the rat using antimony (Sb) as the marker,
- determine the rate and route of excretion of antimony trioxide after oral (PO), intravenous (IV) or intraperitoneal (IP) dosing in the rat,
- contrast absorption kinetics and ability to reach bone marrow after acute PO and IP exposure,
- determine the pattern of tissue distribution and excretion following acute and repeated PO exposure.

## 2.2 Applicable guidelines

The study was conducted in accordance with the OECD Guideline no. 417 (Guideline for Testing of Chemicals, Toxicokinetics, adopted 4 April 1984) and the EU guideline B36 on Toxicokinetics.

The study was conducted in compliance with the Organisation for Economic Co-operation and Development Principles of Good Laboratory Practice (as revised in 1997), Paris, ENV/MC/CHEM(98)17.

# 3 Deviations

There were no deviations from the study plan.

# 4 Materials and methods

## 4.1 Study substances

### *4.1.1 Antimony trioxide (test substance)*

| | |
|---|---|
| Chemical name | : Antimony trioxide |
| Company name | : Campine N |
| Molecular formula | : $Sb_2O_3$ |
| Molecular weight | : 291.5 |
| CAS Reg no. | : 1309-64-4 |
| Batch number | : 29113 |
| Purity | : 99.93 % |
| Appearance | : white powder |
| Storage conditions | : ambient temperature in tightly closed containers |
| Supplier | : Campine n.v. |
| Arrival at TNO | : 11 April 2005 |
| Expiry date | : 1 November 2009 |
| TNO dispense number | : 0500A1 |
| Certificate of Analysis | : Appendix 1 |

### *4.1.2 Antimony trichloride (reference substance)*

| | |
|---|---|
| Chemical name | : Antimony trichloride |
| Molecular formula | : $SbCl_3$ |
| Molecular weight | : 228.1 |
| CAS Reg no. | : 10025-91-9 |
| Lot number | : 07320LC |
| Purity | : 99.99% |
| Appearance | : white powder |
| Storage conditions | : ambient temperature in tightly closed containers |
| Supplier | : Aldrich |
| Product number | : 337374 |
| Arrival at TNO | : 7 July 2005 |
| Expiry date | : 31 July 2010 |
| TNO CBS number | : 46459 |

## 4.2 Test system

### *4.2.1 Animals*

| | |
|---|---|
| Species | Rat |
| Strain | Sprague Dawley Crl:CD (SD) |
| Justification | Laboratory rats are standard rodent species used for studies of this type. The strain was selected based on previous toxicity studies with the test substance. |
| Source | Charles River Deutschland, Sulzfeld, Germany. |
| Number and sex | 27 males and 19 females. In order to take into account unforeseen complications, extra animals were included during the acclimatization period. Four non-dosed animals of each sex were used for blank urine and faeces (24 h collection) and for blank tissue samples. These samples were also used for method validation. |
| Age | 7 weeks of age at the start of dosing. |

### *4.2.2 Maintenance of animals*

| | |
|---|---|
| Acclimatization | Animals were acclimatized to laboratory conditions for at least 5 days prior to the experimental start date, including one day of simulated test conditions in the metabolism cages. |
| Health condition | Upon arrival (13 July 2005), the rats were housed under quarantine conditions and checked for overt signs of ill health and anomalies. Serological investigation of the microbiological status, conducted in random samples, demonstrated that the animals were in good health. |
| Environment | The animals were kept in room 5.2.01, ventilated with 9-11 air changes per hour and maintained at a temperature of 22 +/- 3 ºC and a relative humidity of at least 30% and not exceeding 70% other than during room cleaning. Lighting was artificial with a sequence of 12 hours light and 12 hours dark. |
| Housing | Until the start of dosing, the animals were housed 3-4 per cage (Macrolon type IV) on sawdust. During dosing and collection of excreta, they were housed individually in Nalgene metabolism cages (Techniplast). |
| Identification | The animals were identified by a group letter and a unique animal number on the tail, which was used for sample identification. The cages were identified by cage cards showing the study number, group letter and animal number. |
| Diet | The animals were allowed to have free access to a commercial rodent diet (Rat no. 3 breeding diet, SDS, Special Diets services, Whitham, England). During acclimatization, the rats received batch number 4428 (chow) and in the |

metabolism cages batch number 4544 (powder). The certificates of analysis are given in Appendix 2.

Drinking water

The drinking water was offered ad libitum. The drinking water suitable for human consumption (quality guidelines according to Dutch legislation based on EEC Council Directive 98/83/EEC) was supplied by N.V. Hydron Midden-Nederland. Results of the routine physical, chemical and microbiological examination of drinking water as conducted by the supplier are made available to TNO. In addition, the supplier periodically (twice a year) analyses water samples taken at the premises of TNO Quality of Life in Zeist for a limited number of physical, chemical and microbiological variables. The results of samples taken during or close to the conduct of the study are given in Appendix 3.

## 4.3 Experimental design

The study comprised six groups of rats. The dose levels were selected on the basis of toxicity data. The IV route served as a reference group. Non-dosed animals were used to measure background levels of antimony. An overview of the test groups is given below.

| Time group | Route | Dosing frequency | Dose level | In-life period | Number of animals |
|---|---|---|---|---|---|
| A | IV | single | 1.57 mg/kg $SbCl_3$ | 3 days | 4♂ |
| B | IP | single | 100 mg/kg $Sb_2O_3$ | 3 days | 4♂ |
| C | PO | single | 100 mg/kg $Sb_2O_3$ | 3 days | 4♂ + 4♀ |
| D | PO | single | 1000 mg/kg $Sb_2O_3$ | 3 days | 4♂ + 4♀ |
| E | PO | 14 day repeated | 1000 mg/kg $Sb_2O_3$ | 14 + 3 days | 4♂ + 4♀ |
| F | Control | non-dosed | | 1 day | 4♂ + 4♀ |

### *4.3.1 Sampling*

Group A: Blood samples (tail blood 100 µl) were collected 15, 30 and 60 minutes, and 2, 4, 8, 24 and 48 hours after dosing. At sacrifice (72 hours) blood was collected from the abdominal aorta.
Urine and faeces were collected 0-24, 24-48 and 48-72 h after dosing.
At sacrifice, bone marrow along with left and right femurs were collected.

Group B: Blood samples (tail blood 100 µl) were collected 4, 8, 12, 24 and 48 hours after dosing. At sacrifice (72 hours) blood was collected from the abdominal aorta.
Urine and faeces were collected 0-24, 24-48 and 48-72 h after dosing.
At sacrifice, bone marrow along with left and right femurs were collected.

*The remaining carcasses of groups A and B were stored frozen (< -18ºC) for possible later analysis of organs or tissues of interest. It was decided that additional analysis were not necessary*

Groups C and D: Blood samples (tail blood 100 µl) were collected 4, 8, 12, 24 and 48 hours after dosing. At sacrifice (72 hours) blood was collected from the abdominal aorta.
Urine and faeces were collected 0-24, 24-48 and 48-72 h after dosing.
At sacrifice, the following organs or tissues were collected:

| | | |
|---|---|---|
| Liver | Brain | Femur |
| Kidneys | Thyroid | Blood |
| Lungs | Testes or uterus | Muscle |
| Heart | Prostate or ovaries | Skin |
| Spleen | Bone marrow | Residual carcass |

GI-tract including contents

Group E: Blood samples (tail blood 100 µl) were collected prior to dosing on day 2, 7, 10, 12, 14, and 24 and 48 hours after the final dose on day 14. At sacrifice (72 hours after the final dose) blood was collected from the abdominal aorta.
Urine was collected during the entire period in 24-hour intervals.
At sacrifice, the following organs or tissues were collected:

| | | |
|---|---|---|
| Liver | Brain | Femur |
| Kidneys | Thyroid | Blood |
| Lungs | Testes or uterus | Muscle |
| Heart | Prostate or ovaries | Skin |
| Spleen | Bone marrow | Residual carcass |
| GI-tract including contents | | |

Group F: Control animals were kept for one day in metabolic cages in order to collect blank urine and faeces.
At sacrifice (24 hours) blood was collected from the abdominal aorta. In addition, the following organs or tissues were collected:

| | | |
|---|---|---|
| Liver | Brain | Femur |
| Kidneys | Thyroid | Blood |
| Lungs | Testes or uterus | Muscle |
| Heart | Prostate or ovaries | Skin |
| Spleen | Bone marrow | Residual carcass |
| GI-tract including contents | | |

## 4.4 Conduct of the study

### *4.4.1 Preparation of dose formulations*

*IV dose solution:* The reference substance ($SbCl_3$) was formulated as a solution in sterile isotonic saline solution. The Sb concentration in the dose solution was determined by ICP-AES in aliquots taken prior to and directly after dosing.

*Oral and IP dose formulations:* The test substance ($Sb_2O_3$) was formulated as a suspension in 0.5% hydroxypropyl methylcellulose (w/v) and 0.1% aqueous polysorbate 80 (w/v). The Sb concentration in the dose formulations was determined by ICP-AES in aliquots taken prior to and directly after dosing.

For group E two dose formulations were prepared. The first was used on day 1-7, the second on day 8-14. The dose formulations were gently stirred using a magnetic stirring bar and visually checked for homogeneity before each administration. The Sb concentration in the dose formulations was checked by taking aliquots just before and directly after dosing. In addition, the vehicle used for IP and PO administration was analyzed for any antimony present.

### *4.4.2 Dose administration*

IV administration: Intravenous injection of 5 ml/kg BW in the tail vein.

IP administration: Intraperitoneal dose administered by injection in the abdomen at 10 ml/kg BW.

PO administration: Oral (gavage) dose of 10 ml/kg BW administered by stomach tube

Amount dosed — Before dose administration, the animals were weighed and the dosing amount calculated. The exact dose was determined retrospectively by the difference in weight of the needle plus syringe or stomach tube before and after administration of the formulated test substance. For group E (repeated dose), the administered dose was based on volume. To verify the proper dose administration, the doses were also weighed on day 1, 8 and 14. For each rat, the administered dose and time of dosing was recorded.

*4.4.3 Feeding status and observations*

Feeding status — Rats were allowed to have free access to food and water during their stay in metabolism cages. The animals were not fasted overnight prior to dosing. Administration of the test material was around 9.00 AM.

Animal behaviour — Any unusual behaviour of the animals was recorded.

Body weight — Individual body weights were determined at the start of the acclimatization to the metabolism cages, just before dosing and at sacrifice. Animals of group E were weighed daily prior to dosing.

*4.4.4 Sample collection and storage*

Samples were collected as described in section 4.3.1. All weights were recorded to ensure a proper mass balance

Urine — Urine was collected at room temperature. The samples were weighed, transferred to storage vials and kept frozen (<-18ºC) until analysis.

Faeces — Faeces were collected at room temperature. The faeces were diluted with water and homogenized at the end of the collection period. The homogenate was weighed, transferred to storage vials and kept frozen (<-18ºC) until analysis.

Blood — Blood for blood kinetics was taken from the tail vein (vena sacralis media) by cutting the tip of the tail. Blood (100 µl) was collected in haematocrit capillaries and directly transferred into weighed Eppendorf cups containing 400 µl isotonic saline. Terminal blood was taken from the abdominal aorta and collected in heparinized tubes. After removal of whole blood aliquots, plasma was prepared by centrifugation at approximately 1200xg. Whole blood and the remaining plasma were transferred to storage vials and kept frozen (<-18ºC) until analysis. The blood cells were discarded.

Sacrifice — At the defined time points, the animals were killed by exsanguination after anaesthesia with $CO_2/O_2$, and tissues and organs removed, weighed and kept frozen (<-18ºC) until analysis. The residual carcass and GI-tract were directly digested with aqua regia and stored at room temperature until analysis.

| | |
|---|---|
| Cage wash | At the end of the collection period, cages were rinsed thoroughly with water/Triton X-100 (100/1; v/v). Samples were kept at room temperature until analysis. |
| Identification of samples | Each sample was identified by study number, animal number, sample type, and sampling time and date. In addition, samples received a unique serial number 6502/Xnnn, where X is the type of sample. A sampling list was used to describe the coupling to the original samples. |

*4.4.5 Analysis*

*4.4.5.1 Analysis of Antimony*

***Faeces and dose formulations***

The amount of antimony in samples of faeces homogenates and dose formulations was determined by ICP-AES at a wavelength of 206 nm after destruction with aqua regia. The concentration of antimony was also determined at an alternative wavelength of 217 nm. The difference between the concentrations at these two wavelengths was considered to be not significant if it was smaller than 10 %.

Faeces

- approximately 4-5 g of faeces homogenate was weighed in a 100 ml flask
- 6 ml hydrochloric acid and 2 ml nitric acid were added and the mixture heated on a hotplate during 1 hour
- the solution was transferred to a polyethylene bottle with water and brought to approximately 50 g with water
- the Sb content was determined in the solution by ICP-AES using a calibration line of 0, 0.5, 1, 5, 10, 25 and 50 mg Sb/L

Dose formulations

- 9 ml hydrochloric acid and 3 ml nitric acid were added to weighed aliquots of the dose formulations
- the mixture was heated on a hotplate during 1 hour
- the solution was transferred to a polyethylene bottle with water and brought to approximately 100 and 500 g with water for the low and high dose formulations, respectively
- the Sb content was determined in the solution by ICP-AES ICP-AES using a calibration line of 0, 0.5, 1, 5, 10, 25 and 50 mg Sb/L
-

The following equipment and conditions were used:

| | |
|---|---|
| Instrument model: | IRIS Intrepid |
| Software: | TEVA version 1.4.2 |
| Auto sampler: | Timberline |
| Number of repeats: | 3 |
| Wavelength: | 206, 217 nm (206 nm was used for quantification) |

***Urine, blood and tissues***

The amount of antimony in samples of blood, plasma, urine, cage wash and tissue was determined by analysis with ICP-MS at a mass of 121, including the internal standard rhodium (mass 103) after sample destruction with aqua regia. The Sb concentration was also determined at the alternative mass of 123. The difference between the

concentrations at these two masses was considered not to be significant if it was smaller than 10 %. Prior to ICP-MS analysis, a calculated amount of the internal standard rhodium was added to all solutions.

Urine and cage wash
- approximately 1 g of urine or cage wash was weighed in a 10 ml tube
- the sample was diluted with 9 ml aqua regia and the total solution weighed
- the Sb content was determined in the solution by ICP-MS using a ICP-AES using acalibration line of 0, 0.5, 1, 2, 5, 10, 25, 50, 100 and 200 µg Sb/L

Blood
- the total sample of blood was mixed with 10 ml aqua regia and the total solution weighed
- the mixture was heated on a water bath (boiling) for 1 hour
- the Sb content was determined in the solution by ICP-MS using a ICP-AES using a calibration line of 0, 0.5, 1, 2, 5, 10, 25, 50, 100 and 200 µg Sb/L

Tissue
- a sufficient amount of aqua regia was added to the total sample of tissue to completely immerse the sample
- the mixture was heated on a hotplate during 1 hour or more (residual carcass) to completely break down the sample
- the solution was transferred to a polyethylene bottle with water and brought to an exact mass with water.
- the Sb content was determined in the solution by ICP-MS using a ICP-AES using a calibration line of 0, 0.5, 1, 2, 5, 10, 25, 50, 100 and 200 µg Sb/L

The following equipment and conditions were used:

| | |
|---|---|
| Instrument model: | PerkinElmer SCIEX Elan DRC II |
| Software: | Elan version 2.4 |
| Auto sampler: | Cetac ASX-510 |
| Readings/repeat: | 1 |
| Number of repeats: | 3 |
| Mass isotopes measured: | Tin m/z =121, 123 (m/z 121 was used for quantification) |
| Sweeps/Reading: | 20 |
| Dwell time: | 50.0 ms |
| Read delay: | 15 s |
| Scan mode: | Peak hopping |

Mass isotope internal standard: Rhodium m/z = 103

*4.4.5.2 Pharmacokinetic analysis*

The average background levels of the non-dosed animals were subtracted before pharmacokinetic analysis. For the IV administation the t=0 value was extrapolated using the distribution half-life till t=1 h. The pharmacokinetic parameters were calculated by non-compartmental regression analysis using a custom-made Excel spreadsheet.

| **Parameter** | **Unit** | **Description** |
|---|---|---|
| $C_{max}$ | (ng/g) | Observed maximal blood concentration. |
| $T_{max}$ | (h) | Time to reach $C_{max}$ |
| $AUC_{(0\text{-}n)}$ | (ng/g*h) | Area under the blood concentration versus time curve up to the last sampling point using the log/linear trapezoidal rule. |
| $AUC_{(0\text{-}infinity)}$ | (ng/g*h) | Total area under the blood concentration curve, calculated as $AUC_{(0\text{-}n)}$.+ Cn/ $k_2$ , where Cn is blood concentration at the last sampling point. |
| $k_2$ | ($h^{-1}$) | Elimination rate constant, calculated by linear regression analysis of the terminal part ($C_{max}$ to last time point) of the log-concentration versus time curve. |
| $T_{1/2\ terminal}$ | (h) | Elimination half-life = ln(2)/ $k_2$. |
| Bioavailability IP dose | (%) | $AUC_{(0\text{-}infinity)}$ [IP]/ $AUC_{(0\text{-}infinity)}$[IV] * Dose [IV] / Dose [IP] * 100 Both doses were first converted to mg Sb/kg |
| Bioavailability PO dose | (%) | $AUC_{(0\text{-}infinity)}$ [PO]/ $AUC_{(0\text{-}infinity)}$[IV] * Dose [IV] / Dose [PO] * 100 Both doses were first converted to mg Sb/kg |

*4.4.5.3 Calculation of results*

Sb figures which were below the limit of determination (LOD) were first converted to % of dose using the LOD figure and than presented as < …%.

# 5 Results

## 5.1 Concentration and homogeneity of dose formulations

The dose formulations prepared on the day of administration remained homogeneous throughout use. An overview of dose formulation concentrations determined shortly before and after dosing is presented in Table 1 below.

Table 1 Concentration and homogeneity of dosing formulations

| Dose group (day of preparation) | Concentration (mg Sb/kg dose formulation) | | | |
|---|---|---|---|---|
| | Before dosing | After dosing | Mean | %CV |
| A | 155.3 | 151.9 | 153.6 | 1.6 |
| B | 7972 | 8349 | 8161 | 3.3 |
| C | 8215 | 8635 | 8425 | 3.5 |
| D | 77310 | 77937 | 77623 | 0.6 |
| E | 75431 | 75316 | 75374 | 0.1 |
| F | No dose | No dose | < 1 | - |

## 5.2 Animal observation and dose administration

The animals were checked for appearance and behaviour during acclimatization, at the time of administration, and at each sampling time. No study- or test substance-related signs of toxicity or unusual behaviour were observed. Body weight gain was normal with no differences between the sexes from the various treatment groups. Individual and mean animal body weights, as well as details of the individual and mean administered dose, are presented in Tables A1 to A10 in Appendix 4.

Doses are expressed as mg Sb/kg body weight and as mg $SbCl_3$/kg body weight (group A) or $Sb_2O_3$/kg body weight (group B-E). The administered dose was close to the intended dose for all animals.

One of the male rats receiving the repeated oral high dose (group D) died as a result of incorrect dosing (into to the lungs) at day 8. Some other animals of group D (nr 54, 58 an 51 had some dark red spots on the longs. Instillation of test substance can be excluded, since the Sb content of the longs from these animals was not elevated as compared to the other animals of this group.

At necropsy it was observed that animals that received the IP dose still had visible residues of test substance in the abdominal cavity and thus, absorption from the dosing site was not complete.

### 5.3 Blood kinetics

The time course for antimony in whole blood was determined after administration in all dose groups. Individual blood concentrations of antimony, expressed as ng Sb/g blood, are presented in Table A11 to A20 in Appendix 5. Figure 1a and 1b below show the logarithmic blood concentration of Sb versus time curves after dosing. Blood kinetic parameters are presented in Table 2.

Figure 1a Blood concentration (ng Sb/g on a logaritmic scale) versus time curves of antimony in male and female rats after intravenous or oral administration.

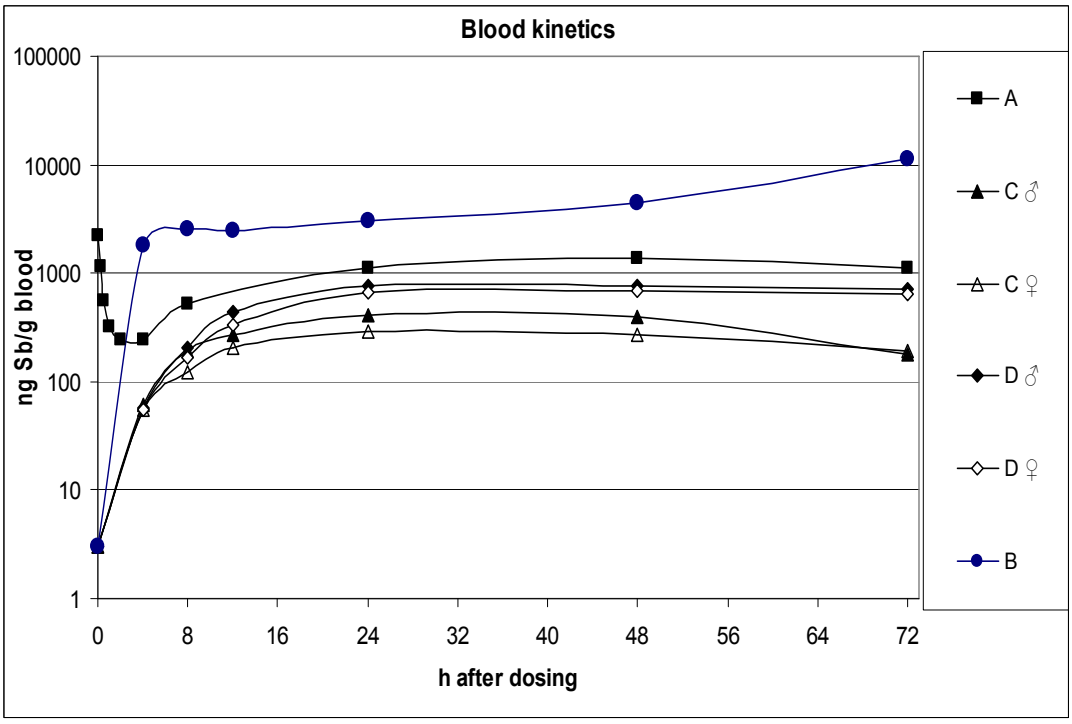
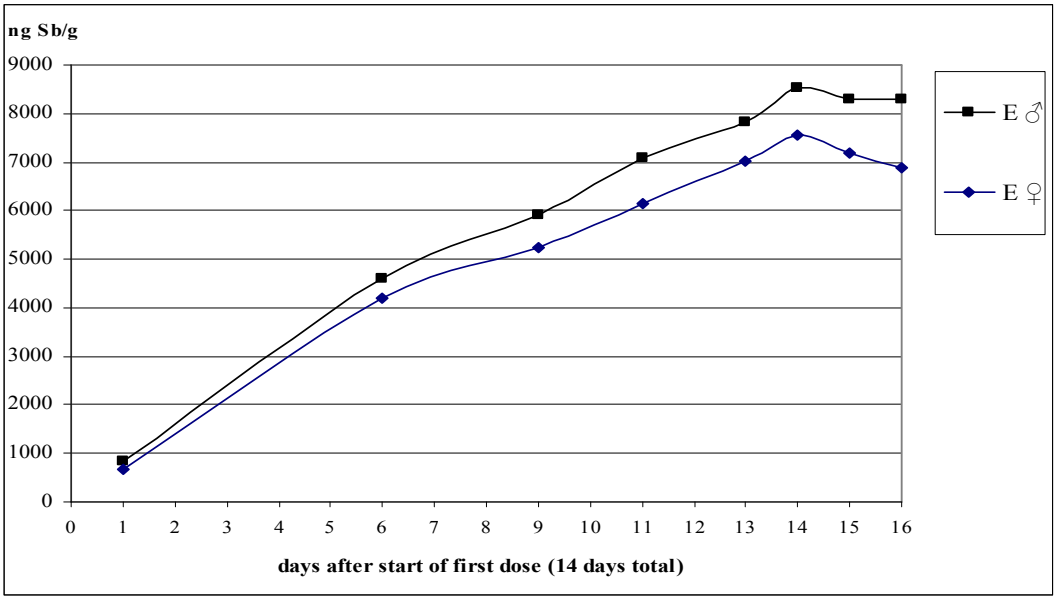



Figure 1b Blood concentration (ng Sb/g on a linear scale) versus time curves of antimony in male and female rats after repeated oral high dosing for 14 days



The blood concentration versus time curve after intravenous injection (group A) showed a rapid distribution phase from the blood into an extravascular compartment. As antimony was injected in a soluble form in this group ($SbCl_3$), it presumably partitioned into the intercellular water just outside of the vascular system. The lowest blood concentration was reached 4 hours after injection. From this time point on, antimony was redistributed to blood and showed a concentration versus time curve very similar to the curve observed after oral administration of $Sb_2O_3$ with an absorption phase and an elimination phase. The $C_{max}$ in blood in this absorption phase was reached approximately 24 hours after dosing both intravenously (Group A) and orally at two concentrations (groups C and D).

The blood concentration versus time curve observed after intraperitoneal injection (group B) presented no clear peak and no elimination phase for the mean of all animals. Individual data (see Table A12 in Appendix 5) show that the blood concentration increased steadily in time for three animals but reached a maximum value at 72h for only two of the four animals (see Appendix 5, Figure A1). In one animal the blood concentration was first very low and then increased suddenly after 48 h. At necropsy it was observed that all animals of the IP group still had visible residues of the test substance in the abdominal cavity indicating that the absorption from the dosing site was not complete. The dosed $Sb_2O_3$, being poorly water soluble, is probably removed only extremely slowly from the peritoneal cavity. The data generated from this group are therefore difficult to interpret and are considered unreliable.

After oral administration (groups C and D), the absorption from the GI-tract into the vascular system was slow, only reaching a peak after ca. 24 hours. The $C_{max}$ was not even two times higher in group D (1000 mg/kg) than in group C (100 mg/kg). The difference between both dose groups for the calculated AUC ($_{0\text{-}72h}$) was in the same range with a ratio between the oral low and high dose of 2 and 1.37 in males and females, respectively. The difference in $C_{max}$ and AUC ($_{0\text{-}72h}$) did not reflect the dose difference indicating that the absorption already had reached a maximum at the low dose.

Table 2 Blood kinetics of Antimony (in ng Sb/g) in rats

| Group | A | B | C | | D | |
|---|---|---|---|---|---|---|
| Sex | male | male | male | female | male | female |
| Dose (mg Sb/kg BW) | 0.752 | 86.8 | 87.3 | 87.2 | 865 | 852 |
| $C_{max}$ (ng/g) | 1353 | 11380 | 400 | 287 | 769 | 680 |
| Tmax (h) | 24 | 72 | 24 | 24 | 24 | 48 |
| $T_{1/2}$ (h) | (83)[2] | n.a. | (21)[2] | (46)[2] | (223)[2] | (253)[2] |
| AUC (0-72h) (ng/g.h) | 73900 | 309000 | 21200 | 28300 | 44400 | 38700 |
| $AUC_{(0\text{-infinity})}$ (ng/g.h) | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| Bioavailability[1] (%) | - | - | 0.247 | 0.330 | 0.052 | 0.046 |

1: Calculated only based on the area under the measured data (AUC 0-72h)
2: Calculated only on the last two measured points and, thus, not reliable
n.a.: not applicable

After the peak, the elimination was also slow for both oral doses and intravenous administration and the half-lives were calculated from elimination rates based on two

time points only (48 and 72h). The $T_{1/2}$ values presented in Table 2 are therefore not considered as sufficiently reliable to allow the extrapolation of the AUC ($_{0\text{-}72h}$) to the $AUC_{(0\text{-infinity})}$. However, a bioavailability factor could be calculated from the AUC ($_{0\text{-}72h}$) of the intravenous and oral groups, which showed that the oral bioavailability of antimony is low but significant in both the low dose (C) and the high dose (D) groups. No sex differences in absorption or distribution were observed in either of the single oral dose groups.

During the 14 days repeated oral high dosing, Sb blood concentrations increased almost linearly with time up to 24 h after the last dose and then decreased slowly (< 5% per day) during the next two days. This indicates that binding to blood cells was not saturated after 14 days at the dose level tested.

## 5.4 Absorption and excretion

The recovery of antimony in urine and faeces was determined in all single dose groups (A to D). Summary results are presented in Table 3 below. Individual data are presented in Table A21 to A26 in Appendix 6. In group A and B, the Sb content in the residual carcass was not determined.

Table 3 Recovery of antimony in excreta and tissues in the various single dose groups- Expressed as % of the dose.

| | Dose group | | | | | |
|---|---|---|---|---|---|---|
| Dose | A | B | C male | C female | D male | D female |
| (mg Sb/kg BW) | 0.752 | 86.1 | 87.3 | 87.2 | 865 | 852 |
| **Urine** 0-24 h | 11.62 | 0.22 | 0.040 | 0.025 | 0.0066 | 0.0061 |
| 24-48 h | 1.57 | 0.10 | 0.003 | 0.006 | 0.0009 | 0.0013 |
| 48-72 h | 0.67 | 0.06 | 0.006 | 0.003 | 0.0004 | 0.0007 |
| **Subtotal** | **13.76** | **0.39** | **0.050** | **0.034** | **0.0079** | **0.0080** |
| **Faeces** 0-24 h | 31.8 | 34.13 | 71.70 | 73.37 | 98.38 | 90.83 |
| 24-48 h | < 7.8 | 1.96 | 7.45 | 8.21 | 1.68 | 7.83 |
| 48-72 h | < 9.1 | 0.18 | 0.09 | 1.75 | 0.01 | 0.07 |
| **Subtotal** | n.a. | 36.26 | 79.23 | 83.33 | 100.07 | 98.74 |
| Cage wash | < 0.61 | 0.01 | < 0.01 | < 0.01 | 0.002 | < 0.001 |
| **Total excreted** | n.a. | 36.67 | 79.29 | 83.37 | 100.08 | 98.75 |
| | | | | | | |
| **GI-tract (incl content** | n.a. | n.a. | 0.004 | 0.019 | 0.002 | 0.003 |
| Tissue residues | | | | | | |
| Excised * | n.a. | n.a. | 0.007 | 0.008 | 0.0043 | 0.0023 |
| Organs | n.a. | n.a. | 0.002 | 0.002 | 0.0003 | 0.0004 |
| Carcass | n.a. | n.a. | 0.023 | 0.021 | 0.0017 | 0.0023 |
| **Total Retained** | n.a. | n.a. | 0.033 | 0.031 | 0.0063 | 0.0051 |
| | | | | | | |
| **Total Recovery** | n.a. | n.a. | 79.33 | 83.42 | 100.09 | 98.76 |

n.a.: not available

* : Sum of blood and tissues (excluding organs)

In the rats of the intravenously $SbCl_3$ dosed group (A), around 30% of the total antimony was excreted in the faeces within the first 24h. Nearly 14% of the dosed Sb was recovered in the urine 72h after dosing. A total above 45% of the dose was excreted at the end of the collection period. Antimony is likely excreted mainly via the bile into the faeces. Therefore the total absorption cannot be calculated from the urine recovery in the orally dosed groups and the bioavailability data as calculated from the blood concentration curves are the most relevant measurement of antimony absorbed from the GI-tract.

In the IP-dosed animals (group B), 36% of the antimony was recovered from the faeces but with a large variability between the animals.
In group C, dosed orally with a single low dose of $Sb_2O_3$, around 80% of the dosed Sb was excreted via the faeces within 72h after dosing. Only very low amounts of antimony were found in the urine (0.05% for males and 0.03% for females) and in the tissues and carcass (0.03%). These results correlate with the oral bioavailability of around 0.3% calculated from the blood concentration curves.

In group D, dosed orally with a single high dose of $Sb_2O_3$, between 99 and 100% was excreted via the faeces within 72h after dosing. Extremely low amounts of Sb were recovered in the urine and the tissues (0.008 and 0.006 % of the dose, respectively). These values correlate with the bioavailability calculated from the blood concentration curves. In both males and females the recovery of Sb in urine and tissues and the calculated bioavailability are approximately 5 to 7 times lower for the high dose group D than for the low dose group C, confirming that the oral absorption reached a maximum.

The urinary excretion of antimony in male and female rats after repeated oral dosing was monitored during the 14 days of the dosing period and for 3 days afterwards. The results are presented in Appendix 6 Table A27 and A28 and graphically in Figure A2 and A3. The excretion was relatively steady in the beginning of the dosing period but seemed to decrease slowly from day 8 on in males and from day 11 on in females. These results might reflect a decrease in antimony absorption from the gastro-intestinal tract rather than a loss of renal excretion capacity because the Sb concentration in the kidneys at sacrifice was not elevated as compared to the carcass (see Table 4). Also a saturation of the system can be excluded since blood concentration of antimony was almost linear, increasing with time. The urinary Sb content decreased rapidly immediately after the last dosing day.

## 5.5 Tissue distribution

In groups A and B, IV- and IP-dosed respectively, the determination of tissue distribution was limited to the blood, plasma, bone marrow and femurs. The results for these groups are presented in Table 4 below and in Tables A29 and A30 in Appendix 7. The distribution of antimony as total Sb is presented in Table 5 for groups C, D, E and F. Individual data are shown in Table A31 to A38 in Appendix 7.

Table 4 Tissue distribution of antimony after a single intravenous dose of $SbCl_3$ or a single intraperitoneal or oral dose of $Sb_2O_3$ in male rats - Expressed as ng Sb/g tissue.

| | A | B | C male |
|---|---|---|---|
| Whole blood | 1111 | 11383 | 181 |
| Plasma | 3.1 | 18 | 3.1 |
| Bone Marrow | 1083 | 40517* | 141 |
| Femurs | 214 | 6081 | 56.4 |

* A wide distribution in values between the four animls was observed (11462-96284)

The ability of antimony to reach bone marrow after a single low dose was around ten times lower in the orally treated rats than in the IV-dosed rats. In the IP-dosed animals, however, the antimony content in bone marrow was approximately four times higher than the blood concentration in these animals and approximately forty times higher than in the bone marrow of the oral low dosed rats.

Table 5 Tissue distribution of antimony after single or repeated oral dosing of $Sb_2O_3$ in rats - Expressed as ng Sb/g tissue.

| | F (control) | | C | | D | | E | |
|---|---|---|---|---|---|---|---|---|
| | **male** | **female** | **male** | **female** | **male** | **female** | **male** | **female** |
| **Whole blood** | **2.8** | **3.0** | **181** | **189** | **708** | **640** | **8278** | **6886** |
| Plasma | 1.8 | 2.8 | 3.1 | 3.2 | 2.8 | 2.6 | 21 | 10 |
| **Bone marrow** | **80** | **142** | **141** | **89** | **1192** | **1996** | **2486** | **3517** |
| Femur | 18.9 | 10.0 | 56 | 38 | 48 | 32 | 254 | 265 |
| Liver | 3.9 | 3.0 | 36 | 25 | 41 | 64 | 823 | 675 |
| Kidney | 2.7 | 2.4 | 15 | 8 | 12 | 23 | 323 | 261 |
| Lung | 3.6 | 2.2 | 36 | 27 | 41 | 61 | 746 | 882 |
| Heart | 3.6 | 3.1 | 22 | 14 | 42 | 41 | 643 | 356 |
| Spleen | 10 | 32 | 83 | 50 | 197 | 113 | 1485 | 1386 |
| Brain | < 1.4 | < 1.4 | 1.4 | < 1.4 | 2.2 | < 1.4 | 30 | 17 |
| **Thyroid** | **98** | **195** | **158** | **120** | **1507** | **2103** | **2639** | **2280** |
| Testes | < 0.8 | n.a. | 2.3 | n.a. | 2.8 | n.a. | 39 | n.a. |
| Prostate | 9.5 | n.a. | 11.4 | n.a. | 8.5 | n.a. | 80 | n.a. |
| Uterus | n.a. | 15.2 | n.a. | 12.8 | n.a. | 11.4 | n.a. | 116 |
| Ovaries | n.a. | 17.3 | n.a. | 29.4 | n.a. | 262 | n.a. | 665 |
| Muscle | 2.7 | 3.3 | 18 | 4.4 | 5.0 | 4.7 | 39 | 44 |
| Skin | 2.3 | 1.5 | 41 | 11 | 9.6 | 16 | 90 | 103 |
| Residual Carcass | 10.4 | 5.7 | 27 | 22 | 19 | 26 | 303 | 221 |

n.a.: not applicable

The Sb concentration in the bone marrow of the control group was higher than the Sb concentration in other tissues and, thus, similar to the Sb concentration in the bone marrow of the oral low dose group (C). But in the oral high dose group (D) the antimony concentration was much higher in bone marrow than in whole blood indicating that appreciable amounts of antimony are deposited in bone marrow. After repeated oral high dosing (group E), the Sb concentration in bone marrow increased less than the concentration in whole blood, which was not the case in group D. This result could indicate a saturation of the bone marrow tissue after repeated dosing.

A similar pattern was seen for the thyroid where the Sb concentration after the single oral low dose was comparable to the control, increased about ten times after a single oral high dose, but did not increase significantly after repeated high dosing. It is noticeable that in control animals the Sb concentration in the thyroid was as high as in the bone marrow and much higher than in whole blood.

The ovaries and spleen showed slightly elevated antimony concentrations after a single oral low dose and a more clear increase after the single oral high dose but the Sb content remained around a factor of 10 above the ovaries and spleen of the control group. The concentrations still increased after repeated oral high dosing but to a much lower extent than in blood.

In most of the other measured organs, such as liver, kidneys and skin, an increase in Sb content was seen after the single oral low dose as compared to the control group, but no major concentration difference was seen between the single oral low and the single oral high dose. The antimony concentration increased significantly (by a factor of 10) only in the repeated oral high dose group.

# 6 Conclusions

*Blood kinetics*
The blood concentration of antimony versus time curve after intravenous injection (Group A) showed a rapid distribution phase from the blood into an extravascular compartment. Antimony was then redistributed back into blood and showed a concentration versus time curve very similar to the curves observed after oral administration of $Sb_2O_3$ in both the low and high dose (groups C and D) with an absorption phase and an elimination phase. After oral administration (groups C and D), the absorption from the GI-tract into the vascular system was slow with a $C_{max}$ at approximately 24 hours after dosing. No accurate half-life could be calculated from the obtained kinetics curves. However, a bioavailability factor was calculated from the AUC ($_{0\text{-}72h}$) of the intravenous and oral dose groups, which showed that the oral bioavailability of antimony is low but significant in both the oral low dose (C) and the oral high dose (D) groups at 0.3% and 0.05%, respectively. It was concluded that the absorption of antimony from the gastro-intestinal tract was a slow and saturable process. The absorption from the dosing site in the IP-dosed group (B) was not complete. The data generated from this group are therefore considered difficult to interpret and unreliable.

*Absorption and excretion*
In the rats of the intravenous group, around 30% of the total antimony was excreted in the faeces within the first 24h and around 14% was recovered in the urine 72h after dosing. In the IP-dosed animals 36% of the antimony was recovered from the faeces whereas in the orally dosed animals around 80% and 100% of the dosed Sb was excreted via the faeces 72h after dosing for the low and the high dose group, respectively. Only very low amounts of antimony were found in the urine, the tissues and carcass in both orally dosed groups. These results correlate with the oral bioavailability of around 0.3% and 0.05% calculated from the blood concentration curves for the low and the high dose group, respectively.

Both the excretion and the calculated bioavailability are 5 to 7 times lower for the oral high dose group (D) than for the oral low dose group (C) confirming that the oral absorption is a saturable process and reached a maximum.

*Bone marrow and tissue distribution*
The ability of antimony to reach bone marrow after a single oral low dose was around ten times lower in the orally treated rats than in the intravenously dosed rats. In the IP-treated animals, however, the Sb content in bone marrow was approximately four times higher than the blood concentration in these animals and approximately forty times higher than in the bone marrow of the oral low dose rats. These results show that the IP route is not adequate to study the tissue distribution of antimony.
The concentration of Sb in the bone marrow of the control group was higher than the Sb concentration in other tissues and similar to the concentration of Sb in the bone marrow of the oral low dose group. But in the oral high dose group the antimony concentration was much higher in bone marrow than in whole blood indicating that appreciable amounts of antimony are deposited into bone marrow. After repeated oral high dosing, the concentration in bone marrow increased less than the concentration in whole blood, which was not seen in the single oral high dose group. This result could indicate a saturation of the bone marrow tissue after repeated oral high dosing.

A similar pattern was seen for the thyroid where the Sb concentration was comparable to the control after a single oral low dose, increased about ten times after a single oral high dose but did not increase significantly after repeated oral high dosing.

In most of the other studied organs the Sb concentration increased moderately after both a single oral low or high dose. After repeated oral dosing, the Sb content was increased in all organs, but not in proportion to the increase in dose.

*Conclusions*
It can be concluded that the absorption of Sb after oral dosing of $Sb_2O_3$ is a slow and saturable process. Sb is poorly absorbed, but undergoes significant distribution as it binds to red blood cells. Appreciable amounts are distributed to bone marrow via all routes of dosing. It can also be concluded that $Sb_2O_3$ undergoes urinary and biliary excretion after oral dosing.

# 7 Documentation and retention of records, samples and specimens

The remaining study substances will be retained for at least six months after submission of the final report. Biological samples will be discarded six months after submission of the final report.

Raw data, the master copy of the final report and all other information relevant to the quality and integrity of the study will be retained in the archives of TNO Quality of Life, Utrechtseweg 48, 3704 HE Zeist for a period of at least 15 years after reporting of the study.

# 8 Appendices

## Appendix 1 Certificate of Analysis of Campine N.

### CERTIFICATE OF ANALYSIS

Inspection certificate DIN 50049/3.1.B ( EN 10204/3.1.B)

**CONTRACT INFORMATION**

Customer: TNO
Contract No:
Quality: Campine N
Article No: 080101
Batch No: 29113
Weight:

**TEST RESULTS**

These values have been taken from measurements made on a production run where this batch is a part of.

| Parameter | Unit | Testmethod | Min. | Max. | Actual |
|---|---|---|---|---|---|
| Total Sb2O3 | % | Internal | 99,80 | | 99,93 |
| Pb | ppm | ICP-OES/XRF | 0 | 1000 | 346 |
| As | ppm | ICP-OES/XRF | 0 | 800 | 341 |
| Fe | ppm | ICP-OES/XRF | 0 | 30 | 9 |
| Average particle size | µm | Fisher | 0,80 | 1,00 | 0,91 |
| Sieve refusal 45 µm | % | ISO 787-7 | 0,000 | 0,010 | 0,005 |

We certify that this product conforms to the relevant Campine product specifications: Rev.01/11-09-2003

07/04/2005

Freddy Smans
quality assurance supervisor

# Appendix 2 Certificate of analysis of the diet

SDS
Special Diets Services

## Special Quality Control Certificate of Analysis

PRODUCT : RM3 (E) SQC
BATCH NO : 4428 DATE OF MANUFACTURE: 28-FEB-05
PREMIX BATCH NO: 13923 DATE OF EXPIRY : 27-NOV-05

| Nutrient | Found Analysis | | Contaminant | Found Analysis | | Limit of Detection |
|---|---|---|---|---|---|---|
| Moisture | 10.6 | % | Fluoride | 15 | mg/kg | 1.0 mg/kg |
| Crude Fat | 5.0 | % | Nitrate as NaNO3 | 42 | mg/kg | 2.0 mg/kg |
| Crude Protein | 23.9 | % | Nitrite as NaNO2 | 2.1 | mg/kg | 1.0 mg/kg |
| Crude Fibre | 4.2 | % | Lead | Non Detected | mg/kg | 0.25 mg/kg |
| Ash | 6.8 | % | Arsenic | 0.20 | mg/kg | 0.2 mg/kg |
| Calcium | 1.18 | % | Cadmium | 0.08 | mg/kg | 0.05 mg/kg |
| Phosphorus | 0.78 | % | Mercury | 0.01 | mg/kg | 0.01 mg/kg |
| Sodium | 0.33 | % | Selenium | 0.38 | mg/kg | 0.05 mg/kg |
| Chloride | 0.62 | % | | | | |
| Potassium | 0.89 | % | | | | |
| Magnesium | 0.22 | % | Total Aflatoxins | Non Detected | mcg/kg | 1 mcg/kg each of B1,B2,G1,G2 |
| Iron | 234 | mg/kg | | | | |
| Copper | 15 | mg/kg | Total P.C.B | Non Detected | mcg/kg | 10.0 mcg/kg |
| Manganese | 75 | mg/kg | Total D.D.T | Non Detected | mcg/kg | 10.0 mcg/kg |
| Zinc | 62 | mg/kg | Dieldrin | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Lindane | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Heptachlor | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Malathion | Non Detected | mcg/kg | 20.0 mcg/kg |
| Vitamin A | 12.9 | iu/g | Total Viable Organisms x 1000 | Non Detected | per grm | 1000/g |
| Vitamin E | 78 | mg/kg | | | | |
| Vitamin C | | mg/kg | Mesophilic Spores x 100 | Non Detected | per grm | 100/g |
| | | | Salmonellae Species | Non Detected | per grm | Absent in 20 grm |
| | | | Entero Bacteriaceae | Non Detected | per grm | Absent in 20 grm |
| | | | Escherichia Coli | Non Detected | per grm | Absent in 20 grm |
| | | | Fungal Units | 30 | per grm | Absent in 20 grm |
| | | | Antibiotic Activity | Non Detected | | |

Signed R S Fluid
Dated 21/03/2005

# Appendix 2 Certificate of analysis of the diet (continued)

SDS
Special Diets Services

## Special Quality Control Certificate of Analysis

PRODUCT : RM3 (E) SQC FG
BATCH NO : 4544 DATE OF MANUFACTURE: 27-APR-05
PREMIX BATCH NO: 13977 DATE OF EXPIRY : 26-JAN-06

| Nutrient | Found Analysis | | Contaminant | Found Analysis | | Limit of Detection |
|---|---|---|---|---|---|---|
| Moisture | 8.6 | % | Fluoride | 20 | mg/kg | 1.0 mg/kg |
| Crude Fat | 4.9 | % | Nitrate as NaNO3 | 20 | mg/kg | 2.0 mg/kg |
| Crude Protein | 22.8 | % | Nitrite as NaNO2 | 2.5 | mg/kg | 1.0 mg/kg |
| Crude Fibre | 4.3 | % | Lead | Non Detected | mg/kg | 0.25 mg/kg |
| Ash | 6.8 | % | Arsenic | 0.20 | mg/kg | 0.2 mg/kg |
| Calcium | 1.29 | % | Cadmium | 0.09 | mg/kg | 0.05 mg/kg |
| Phosphorus | 0.79 | % | Mercury | Non Detected | mg/kg | 0.01 mg/kg |
| Sodium | 0.32 | % | Selenium | 0.28 | mg/kg | 0.05 mg/kg |
| Chloride | 0.58 | % | | | | |
| Potassium | 0.90 | % | | | | |
| Magnesium | 0.22 | % | Total Aflatoxins | Non Detected | mcg/kg | 1 mcg/kg each of B1,B2,G1,G2 |
| Iron | 130 | mg/kg | | | | |
| Copper | 16 | mg/kg | Total P.C.B | Non Detected | mcg/kg | 10.0 mcg/kg |
| Manganese | 87 | mg/kg | Total D.D.T | Non Detected | mcg/kg | 10.0 mcg/kg |
| Zinc | 66 | mg/kg | Dieldrin | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Lindane | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Heptachlor | Non Detected | mcg/kg | 10.0 mcg/kg |
| | | | Malathion | Non Detected | mcg/kg | 20.0 mcg/kg |
| Vitamin A | 13.5 | iu/g | Total Viable Organisms x 1000 | Non Detected | per grm | 1000/g |
| Vitamin E | 77 | mg/kg | | | | |
| Vitamin C | | mg/kg | Mesophilic Spores x 100 | Non Detected | per grm | 100/g |
| | | | Salmonellae Species | Non Detected | per grm | Absent in 20 grm |
| | | | Entero Bacteriaceae | Non Detected | per grm | Absent in 20 grm |
| | | | Escherichia Coli | Non Detected | per grm | Absent in 20 grm |
| | | | Fungal Units | 170 | per grm | Absent in 20 grm |
| | | | Antibiotic Activity | Non Detected | | |

Signed .....
Dated 26/05/2005

# Appendix 3 Certificate of water analysis

Results of periodical analyses in drinking water collected on the premises of TNO Quality of Life in Zeist, the Netherlands.

This is a translation of the Analysis Report of N.V. Hydron Midden-Nederland, dated 9 June 2005.
The analyses were conducted in samples taken on 26 May 2005 (08:50 hr) in room number 05.1.11 at TNO Quality of Life, Utrechtseweg 48, Zeist.

| Parameter | Unit | Measured |
|---|---|---|
| Clarity (qualitative) | | clear |
| Oxygen | mg $O_2$/l | 11,6 |
| pH | | 8.14 |
| Temperature | °C | 19 |
| Non Purgeable Organic Carbon | mg C/l | 0.32 |
| Iron | mg/l | 0.028 |
| Electrical conductivity | mS/m | 25.1 |
| Manganese | mg/l | <0.002 |
| Ammonia | mg N/l | <0.03 |
| Nitrite | mg N/l | <0.002 |
| Nitrate | mg N/l | 1.68 |
| Cadmium | µg/l | <0.5 |
| Copper | µg/l | 57,1 |
| Lead | µg/l | <3 |
| Aeromonas bacteria | #/100 ml | <10 |
| Coli bacteria (37°C) | #/100 ml | <1 |
| Plate count 22°C | #/ml (by approximation) | 30 |

Conclusion:
The above parameters meet the requirements of the Dutch Water Supply Act.

# Appendix 4 Body weights and dose - individual data

Table A1 Body weights and dose of male rats receiving a single intravenous (IV) target dose of 1.57 mg $SbCl_3$/kg BW (group A)

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2 | 4 | 6 | 8 | Mean | SD |
| Body weight (g): | day -1 | 259 | 264 | 264 | 282 | 267 | 10 |
| | day 0 | 266 | 273 | 266 | 293 | 274 | 13 |
| | at sacrifice | 281 | 276 | 274 | 292 | 281 | 8 |
| Dose (mg Sb/kg BW) | | 0.752 | 0.743 | 0.746 | 0.768 | 0.752 | 0.011 |
| Dose (mg $SbCl_3$/kg BW) | | 1.408 | 1.391 | 1.396 | 1.439 | 1.409 | 0.021 |

Table A2 Body weights and dose of male rats receiving a single intraperitoneal (IP) target dose of 100 mg $Sb_2O_3$/kg BW (group B)

| | | | | | | Animal number | |
|---|---|---|---|---|---|---|---|
| | | 12 | 14 | 16 | 18 | Mean | SD |
| Body weight (g): | day-1 | 261 | 290 | 293 | 303 | 287 | 18 |
| | day 0 | 266 | 303 | 306 | 310 | 296 | 20 |
| | at sacrifice | 265 | 297 | 292 | 315 | 292 | 20 |
| Dose (mg Sb/kg BW) | | 86.1 | 86.3 | 87.0 | 87.7 | 86.8 | 0.7 |
| Dose (mg Sb2O3/kg BW) | | 103.1 | 103.3 | 104.2 | 105.0 | 103.9 | 0.9 |

Table A3 Body weights and dose of male rats receiving a single oral (PO) target dose of 100 mg $Sb_2O_3$/kg BW (group C male).

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 22 | 24 | 26 | 28 | Mean | SD |
| Body weight (g): day-1 | 266 | 278 | 300 | 301 | 286 | 17 |
| day 0 | 274 | 287 | 314 | 312 | 297 | 20 |
| at sacrifice | 280 | 295 | 317 | 310 | 301 | 16 |
| Dose (mg Sb/kg BW) | 87.7 | 81.7 | 91.7 | 88.2 | 87.3 | 4.2 |
| Dose (mg $Sb_2O_3$/kg BW) | 104.9 | 97.8 | 109.8 | 105.6 | 104.6 | 5.0 |

Table A4 Body weights and dose of female rats receiving a single oral (PO) target dose of 100 mg $Sb_2O_3$/kg BW (group C female).

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 21 | 23 | 25 | 27 | Mean | SD |
| Body weight (g): day-1 | 200 | 206 | 185 | 205 | 199 | 10 |
| day 0 | 200 | 208 | 175 | 210 | 198 | 16 |
| at sacrifice | 202 | 203 | 189 | 209 | 201 | 8 |
| Dose (mg Sb/kg BW) | 87.0 | 87.0 | 86.3 | 88.7 | 87.2 | 1.0 |
| Dose (mg $Sb_2O_3$/kg BW) | 104.1 | 104.1 | 103.3 | 106.2 | 104.4 | 1.2 |

Table A5 Body weights and dose of male rats receiving a single oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group D male).

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 32 | 34 | 36 | 38 | Mean | SD |
| Body weight (g): | day-1 | 300 | 281 | 291 | 273 | 286 | 12 |
| | day 0 | 306 | 282 | 294 | 281 | 291 | 12 |
| | at sacrifice | 299 | 276 | 298 | 288 | 290 | 11 |
| Dose (mg Sb/kg BW) | | 881 | 856 | 844 | 879 | 865 | 18 |
| Dose (mg $Sb_2O_3$/kg BW) | | 1054 | 1025 | 1010 | 1053 | 1036 | 22 |

Table A6 Body weights and dose of male rats receiving a single oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group D female).

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 31 | 33 | 35 | 37 | Mean | SD |
| Body weight (g): | day-1 | 204 | 200 | 192 | 203 | 200 | 5 |
| | day 0 | 204 | 188 | 200 | 204 | 199 | 8 |
| | at sacrifice | 205 | 198 | 201 | 197 | 200 | 4 |
| Dose (mg Sb/kg BW) | | 835 | 882 | 838 | 852 | 852 | 22 |
| Dose (mg $Sb_2O_3$/kg BW) | | 999 | 1056 | 1003 | 1020 | 1020 | 26 |

Table A7 Body weights and dose of male rats receiving a 14 day repeated oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group E male).

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 52 | 54 | 56 | 58 | Mean | SD |
| Body weight (g): | day-1 | 259 | 261 | 264 | 276 | 265 | 8 |
| | day 0 | 265 | 274 | 271 | 286 | 274 | 9 |
| | day 1 | 266 | 273 | 270 | 289 | 275 | 10 |
| | Day 2 | 275 | 275 | 273 | 292 | 279 | 9 |
| | Day 3 | 268 | 282 | 273 | 298 | 280 | 13 |
| | Day 4 | 274 | 288 | 272 | 302 | 284 | 14 |
| | Day 5 | 285 | 296 | 275 | 306 | 291 | 13 |
| | Day 6 | 287 | 296 | 271 | 311 | 291 | 17 |
| | Day 7 | 288 | 303 | 259 | 308 | 290 | 22 |
| | Day 8 | 290 | 304 | - | 312 | 302 | 11 |
| | Day 9 | 291 | 305 | - | 313 | 303 | 11 |
| | Day 10 | 295 | 310 | - | 318 | 308 | 12 |
| | Day 11 | 303 | 321 | - | 321 | 315 | 10 |
| | Day 12 | 304 | 324 | - | 323 | 317 | 11 |
| | Day 13 | 310 | 327 | - | 328 | 322 | 10 |
| | at sacrifice | 316 | 336 | - | 339 | 330 | 13 |
| Last dose (mg Sb/kg BW) | | 670 | 764 | | 752 | 729 | 51 |
| Last dose (mg $Sb_2O_3$/kg BW) | | 802 | 915 | | 901 | 873 | 61 |

- : no data available because the animal died

Table A8 Body weights and dose of female rats receiving a 14 day repeated oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group E female)

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 51 | 53 | 55 | 57 | Mean | SD |
| Body weight (g): | day-1 | 188 | 199 | 205 | 213 | 201 | 11 |
| | day 0 | 206 | 181 | 187 | 214 | 197 | 16 |
| | day 1 | 207 | 198 | 194 | 217 | 204 | 10 |
| | Day 2 | 210 | 202 | 196 | 217 | 206 | 9 |
| | Day 3 | 218 | 209 | 200 | 222 | 212 | 10 |
| | Day 4 | 215 | 213 | 194 | 218 | 210 | 11 |
| | Day 5 | 224 | 213 | 197 | 226 | 215 | 13 |
| | Day 6 | 225 | 217 | 211 | 227 | 220 | 7 |
| | Day 7 | 225 | 220 | 212 | 224 | 220 | 6 |
| | Day 8 | 227 | 219 | 217 | 225 | 222 | 5 |
| | Day 9 | 224 | 218 | 219 | 227 | 222 | 4 |
| | Day 10 | 231 | 226 | 226 | 232 | 229 | 3 |
| | Day 11 | 234 | 234 | 230 | 242 | 235 | 5 |
| | Day 12 | 233 | 235 | 237 | 242 | 237 | 4 |
| | Day 13 | 238 | 237 | 241 | 238 | 239 | 2 |
| | at sacrifice | 238 | 245 | 254 | 253 | 248 | 8 |
| Last dose (mg Sb/kg BW) | | 766 | 766 | 765 | 757 | 764 | 4 |
| Last dose (mg $Sb_2O_3$/kg BW) | | 917 | 918 | 916 | 907 | 914 | 5 |

Table A9 Body weights of control group male rats (group F male)

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 62 | 64 | 66 | 68 | Mean | SD |
| Body weight (g): | day-1 | 260 | 261 | 270 | 270 | 265 | 6 |
| | day 0 | 269 | 255 | 273 | 268 | 266 | 8 |
| | at sacrifice | 279 | 266 | 282 | 280 | 277 | 7 |
| Dose (mg Sb/kg BW) | | n/a | n/a | n/a | n/a | n/a | n/a |
| Dose (mg $Sb_2O_3$/kg BW) | | n/a | n/a | n/a | n/a | n/a | n/a |

Table A10 Body weights of control group female rats (group F female)

.

| | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 61 | 63 | 65 | 67 | Mean | SD |
| Body weight (g): | day-1 | 193 | 196 | 206 | 211 | 202 | 8 |
| | day 0 | 195 | 196 | 213 | 210 | 204 | 9 |
| | at sacrifice | 194 | 198 | 197 | 209 | 200 | 7 |
| Dose (mg Sb/kg BW) | | n/a | n/a | n/a | n/a | n/a | n/a |
| Dose (mg $Sb_2O_3$/kg BW) | | n/a | n/a | n/a | n/a | n/a | n/a |

n/a: not applicable

# Appendix 5 Blood kinetics – individual data

Table A11 Concentration of antimony in blood samples from male rats after a single intravenous (IV) target dose of 1.57 mg $SbCl_3$/kg BW (group A) Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 2 | 4 | 6 | 8 | Mean | SD |
| (mg Sb/kg BW) | 0.752 | 0.743 | 0.746 | 0.768 | 0.752 | 0.011 |
| (mg $SbCl_3$/kg BW) | 1.408 | 1.391 | 1.396 | 1.439 | 1.409 | 0.021 |
| Time after dosing | | | | | | |
| 0.25 h | 734 | 1504 | 1343 | 982 | 1141 | 348 |
| 0.5 h | 320 | 589 | 703 | 651 | 566 | 170 |
| 1 h | 222 | 291 | 366 | 398 | 319 | 79 |
| 2 h | 169 | 201 | 256 | 336 | 241 | 73 |
| 4 h | 212 | 215 | 272 | 280 | 245 | 36 |
| 8 h | 378 | 495 | 587 | 631 | 523 | 112 |
| 24 h | 805 | 1101 | 1362 | 1244 | 1128 | 240 |
| 48 h | 973 | 1301 | 1660 | 1492 | 1356 | 295 |
| 72 h | 923 | 1325 | 1158 | 1039 | 1111 | 172 |

Table A12 Concentration of antimony in blood samples from male rats after a single intraperitoneal (IP) target dose of 100 mg $Sb_2O_3$/kg BW (group B). Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 12 | 14 | 16 | 18 | Mean | SD |
| (mg Sb/kg BW) | 86.1 | 86.3 | 87.0 | 87.7 | 86.8 | 0.7 |
| (mg $Sb_2O_3$/kg BW) | 103.1 | 103.3 | 104.2 | 105.0 | 103.9 | 0.9 |
| Time after dosing | | | | | | |
| 4 h | 2946 | 1353 | 2904 | 75 | 1819 | 1379 |
| 8 h | 5429 | 1460 | 3262 | 89 | 2560 | 2312 |
| 12 h | 4121 | 1813 | 3866 | 110 | 2477 | 1887 |
| 24 h | 3082 | 2470 | 6549 | 133 | 3059 | 2651 |
| 48 h | 6228 | 2566 | 8622 | 113 | 4382 | 3782 |
| 72 h | 3884 | 2365 | 26505 | 12776 | 11383 | 11078 |

Figure A1: Concentration of antimony in blood samples from male rats after a single intraperitoneal (IP) target dose of 100 mg $Sb_2O_3$/kg BW (group B). Expressed as ng Sb/g blood.

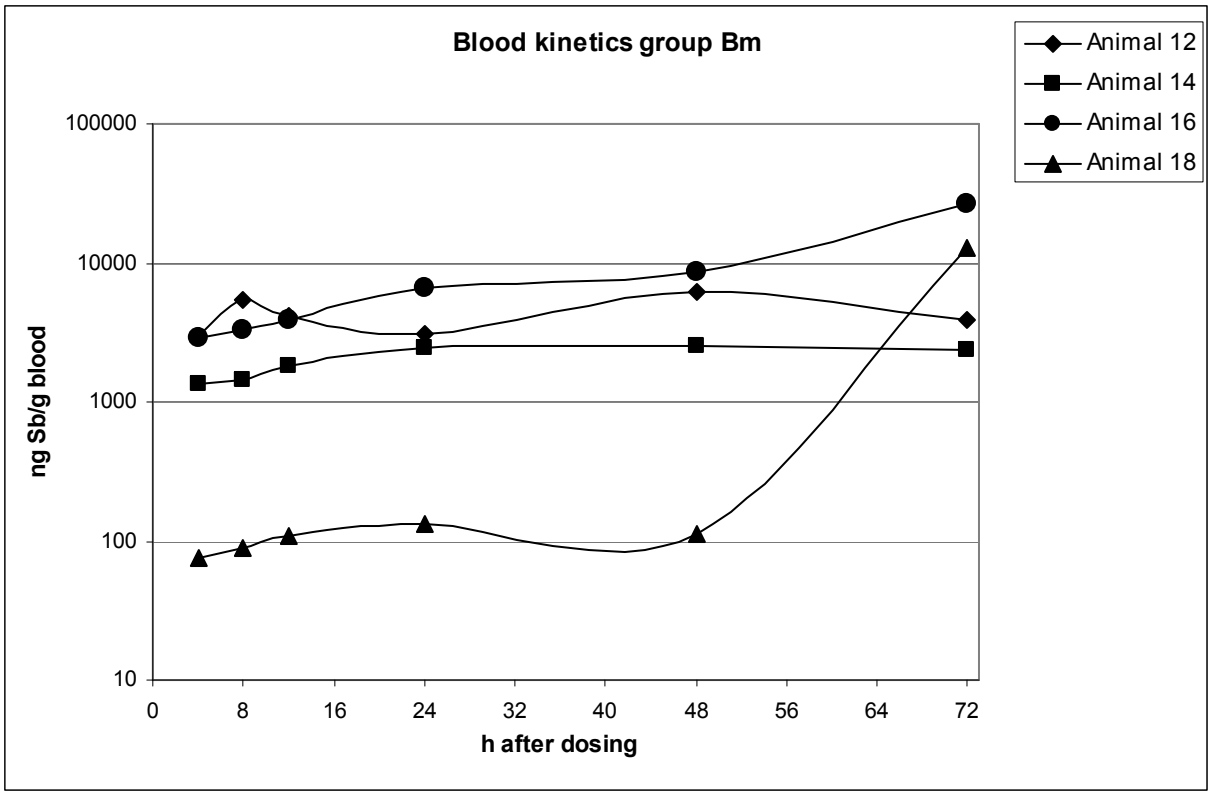


Table A13 Concentration of antimony in blood samples from male rats after a single oral (PO) target dose of 100 mg $Sb_2O_3$/kg BW (group C male).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 22 | 24 | 26 | 28 | Mean | SD |
| (mg Sb/kg BW) | 87.7 | 81.7 | 91.7 | 88.2 | 87.3 | 4.2 |
| (mg $Sb_2O_3$/kg BW) | 104.9 | 97.8 | 109.8 | 105.6 | 104.6 | 5.0 |
| Time after dosing | | | | | | |
| 4 h | 58 | 60 | 52 | 72 | 61 | 8 |
| 8 h | 141 | 316 | 132 | 171 | 190 | 86 |
| 12 h | 214 | 375 | 236 | 260 | 271 | 72 |
| 24 h | 264 | 480 | 393 | 477 | 403 | 101 |
| 48 h | 248 | 523 | 392 | 433 | 399 | 115 |
| 72 h | 171 | 172 | 54 | 325 | 181 | 111 |

Table A14 Concentration of antimony in blood samples from female rats after a single oral (PO) target dose of 100 mg/kg $Sb_2O_3$ BW(group C female).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 21 | 23 | 25 | 27 | Mean | SD |
| (mg Sb/kg BW) | 87.0 | 87.0 | 86.3 | 88.7 | 87.2 | 1.0 |
| (mg $Sb_2O_3$/kg BW) | 104.1 | 104.1 | 103.3 | 106.2 | 104.4 | 1.2 |
| Time after dosing | | | | | | |
| 4 h | 35 | 70 | 47 | 65 | 54 | 16 |
| 8 h | 121 | 141 | 88 | 132 | 121 | 23 |
| 12 h | 197 | 240 | 116 | 272 | 206 | 68 |
| 24 h | 270 | 323 | 141 | 425 | 290 | 118 |
| 48 h | 307 | 290 | 129 | 350 | 269 | 97 |
| 72 h | 201 | 214 | 87 | 254 | 189 | 71 |

Table A15 Concentration of antimony in blood samples from male rats after a single oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group D male).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 32 | 34 | 36 | 38 | Mean | SD |
| (mg Sb/kg BW) | 881 | 856 | 844 | 879 | 865 | 18 |
| (mg $Sb_2O_3$/kg BW) | 1054 | 1025 | 1010 | 1053 | 1036 | 22 |
| Time after dosing | | | | | | |
| 4 h | 50 | 57 | 60 | 59 | 56 | 5 |
| 8 h | 175 | 189 | 284 | 160 | 202 | 56 |
| 12 h | 392 | 420 | 577 | 362 | 438 | 96 |
| 24 h | 746 | 675 | 942 | 724 | 772 | 117 |
| 48 h | 779 | 730 | 918 | 622 | 762 | 123 |
| 72 h | * | 718 | 865 | 539 | 707 | 163 |

* a value of 2154 ngSb/g was found which was considered as an outlier or mistake in determination, value not use for calculation of mean and SD

Table A16 Concentration of antimony in blood samples from female rats after a single oral (PO) target dose of 1000 mg $Sb_2O_3$/kg BW (group D female).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| Dose | 31 | 33 | 35 | 37 | Mean | SD |
| (mg Sb/kg BW) | 835 | 882 | 838 | 852 | 852 | 22 |
| (mg $Sb_2O_3$/kg BW) | 999 | 1056 | 1003 | 1020 | 1020 | 26 |
| Time after dosing | | | | | | |
| 4 h | 55 | 49 | 43 | 72 | 55 | 13 |
| 8 h | 158 | 187 | 136 | 197 | 169 | 28 |
| 12 h | 310 | 319 | 293 | 399 | 330 | 47 |
| 24 h | 481 | 577 | 713 | 865 | 659 | 167 |
| 48 h | 492 | 666 | 675 | 897 | 683 | 166 |
| 72 h | 481 | 601 | 652 | 823 | 639 | 142 |

Table A17 Concentration of antimony in blood samples from male rats after 14 days repeated oral dosing of 1000 mg $Sb_2O_3$/kg BW (group E male).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 52 | 54 | 56 | 58 | Mean | SD |
| Time after dosing | | | | | | |
| Day 1 | 968 | 688 | * | 829 | 829 | 140 |
| Day 6 | 5349 | 3876 | * | 4614 | 4613 | 737 |
| Day 9 | 6382 | 5085 | * | 6247 | 5905 | 713 |
| Day 11 | 7396 | 6208 | * | 7647 | 7083 | 769 |
| Day 13 | 8100 | 6849 | * | 8500 | 7816 | 861 |
| Day 14 | 8618 | 7766 | * | 9189 | 8525 | 716 |
| Day 15 | 8334 | 7565 | * | 8940 | 8280 | 689 |
| Day 16 | 8135 | 7626 | * | 9074 | 8278 | 735 |

* animal died

Table A18 Concentration of antimony in blood samples from female rats after 14 days repeated oral dosing of 1000 mg $Sb_2O_3$/kg BW (group E female).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 51 | 53 | 55 | 57 | Mean | SD |
| Time after dosing | | | | | | |
| Day 1 | 637 | 640 | 745 | 713 | 684 | 54 |
| Day 6 | 3733 | 4526 | 4215 | 4351 | 4206 | 340 |
| Day 9 | 5003 | 5984 | 5429 | 4596 | 5253 | 594 |
| Day 11 | 5901 | 6839 | 5757 | 6123 | 6155 | 480 |
| Day 13 | 7195 | 7079 | 6880 | 6922 | 7019 | 145 |
| Day 14 | 7355 | 7900 | 7194 | 7716 | 7541 | 324 |
| Day 15 | 7557 | 7431 | 6876 | 6850 | 7179 | 368 |
| Day 16 | 7552 | 7031 | 6744 | 6218 | 6886 | 557 |

Table A19 Concentration of antimony in blood and plasma samples from control male rats (group F male).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 62 | 64 | 66 | 68 | Mean | SD |
| Whole blood | 3.0 | 2.6 | 2.8 | 2.7 | 2.8 | 0.2 |
| Plasma | 1.9 | 1.7 | 1.6 | 2.1 | 1.8 | 0.2 |

Table A20 Concentration of antimony in blood samples from control female rats (group F female).
Expressed as ng Sb/g blood.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 61 | 63 | 65 | 67 | Mean | SD |
| Whole blood | 3.1 | 2.7 | 3.4 | 2.6 | 3.0 | 0.4 |
| Plasma | 3.1 | 3.5 | 2.3 | 2.4 | 2.8 | 0.6 |

# Appendix 6 Recovery in tissues and excreta – individual data

Table A21 Recovery of antimony in excreta and tissues from male rats after a single intravenous (IV) dose of 1.57 mg $SbCl_3$/kg BW (group A). Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 2 | 4 | 6 | 8 | Mean | SD |
| mg Sb/kg BW | | 0.752 | 0.743 | 0.746 | 0.768 | 0.752 | 0.011 |
| mg $Sb_2O_3$/kg BW | | 1.408 | 1.391 | 1.396 | 1.439 | 1.409 | 0.021 |
| **Urine** | 0- 24 h | 11.79 | 12.17 | 11.99 | 10.52 | 11.62 | 0.75 |
| | 24-48 h | 1.07 | 1.30 | 2.09 | 1.81 | 1.57 | 0.47 |
| | 48-72 h | < 0.33 | 0.82 | 0.82 | 0.71 | 0.67 | 0.23 |
| | **Subtotal** | 13.20 | 14.30 | 14.91 | 13.05 | 13.86 | 0.89 |
| **Faeces** | 0-24 h | 34.9 | 29.9 | 30.2 | 32.3 | 31.8 | 2.3 |
| | 24-48 h | < 9.0 | < 8.2 | < 8.6 | < 7.3 | < 7.8 | n.a. |
| | 48-72 h | < 10.0 | < 8.1 | < 10.0 | < 8.2 | 9.1 | n.a. |
| | **Subtotal** | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. |
| | Cage wash | < 0.58 | < 0.67 | < 0.75 | < 0.45 | < 0.61 | n.a. |
| | | | | | | | |

n.a.: Not available

Table A22 Recovery of antimony from male rats after a single intraperitoneal (IP) dose of 100 mg $Sb_2O_3$/kg BW (group B).
Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 12 | 14 | 16 | 18 | Mean | SD |
| mg Sb/kg BW | | 86.1 | 86.3 | 87.0 | 87.7 | 86.8 | 0.7 |
| mg $Sb_2O_3$/kg BW | | 103.1 | 103.3 | 104.2 | 105.0 | 103.9 | 0.9 |
| **Urine** | 0- 24 h | 0.48 | 0.08 | 0.33 | 0.01 | 0.22 | 0.22 |
| | 24-48 h | 0.23 | 0.03 | 0.16 | < 0.01 | 0.10 | 0.11 |
| | 48-72 h | 0.10 | 0.11 | 0.11 | < 0.01 | 0.08 | 0.05 |
| | **Subtotal** | 0.81 | 0.22 | 0.61 | 0.01 | 0.41 | 0.36 |
| **Faeces** | 0-24 h | 5.62 | 44.91 | 1.06 | 84.93 | 34.13 | 39.17 |
| | 24-48 h | 0.59 | 4.77 | 0.35 | 2.11 | 1.96 | 2.03 |
| | 48-72 h | 0.16 | 0.20 | 0.28 | 0.09 | - | - |
| | **Subtotal** | 6.37 | 49.87 | 1.69 | 87.13 | 36.26 | 40.26 |
| | Cage wash | 0.02 | < 0.01 | 0.01 | < 0.01 | 0.01 | n.a. |
| | | | | | | | |

n.a. : not available

Table A23 Recovery of antimony in excreta and tissues from male rats after a single oral dose of 100 mg $Sb_2O_3$/kg BW (group C male).
Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 22 | 24 | 26 | 28 | Mean | SD |
| mg Sb/kg BW | | 87.7 | 81.7 | 91.7 | 88.2 | 87.3 | 4.2 |
| mg $Sb_2O_3$/kg BW | | 104.9 | 97.8 | 109.8 | 105.6 | 104.6 | 5.0 |
| **Urine** | 0- 24 h | 0.036 | 0.050 | 0.033 | 0.042 | 0.040 | 0.007 |
| | 24-48 h | 0.004 | 0.004 | < 0.002 | 0.004 | 0.003 | 0.001 |
| | 48-72 h | 0.007 | < 0.003 | < 0.003 | 0.012 | 0.006 | 0.004 |
| | **Subtotal** | 0.047 | 0.057 | 0.039 | 0.058 | 0.050 | 0.009 |
| **Faeces** | 0-24 h | 79.87 | 77.18 | 75.46 | 54.28 | 71.70 | 11.76 |
| | 24-48 h | 1.10 | 3.26 | 3.03 | 22.41 | 7.45 | 10.02 |
| | 48-72 h | < 0.08 | < 0.08 | < 0.08 | < 0.08 | < 0.08 | - |
| | **Subtotal** | 81.06 | 80.51 | 78.57 | 76.77 | 79.29 | 1.96 |
| Cage wash | | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | - |
| **Total excreted** | | 81.12 | 80.60 | 78.62 | 76.83 | 79.29 | 1.96 |
| | | | | | | | |
| **GI-tract (incl content** | | 0.005 | 0.004 | 0.003 | 0.002 | 0.004 | 0.001 |
| Tissue residues | | | | | | | |
| Excised * | | 0.008 | 0.008 | 0.002 | 0.012 | 0.008 | 0.004 |
| Organs | | 0.002 | 0.004 | 0.002 | 0.002 | 0.003 | 0.001 |
| Carcass | | 0.036 | 0.034 | 0.014 | 0.006 | 0.023 | 0.015 |
| **Total Retained** | | 0.046 | 0.046 | 0.019 | 0.020 | 0.033 | 0.015 |
| | | | | | | | |
| **Total Recovery** | | 81.17 | 80.65 | 78.64 | 76.86 | 79.33 | 1.98 |

* : Sum of blood and tissues (excluding organs)

Table A24 Recovery of antimony in excreta and tissues from female rats after a single oral dose of 100 mg $Sb_2O_3$/kg BW (group C female).
Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 21 | 23 | 25 | 27 | Mean | SD |
| mg Sb/kg BW | | 87.0 | 87.0 | 86.3 | 88.7 | 87.2 | 1.0 |
| mg $Sb_2O_3$/kg BW | | 104.1 | 104.1 | 103.3 | 106.2 | 104.4 | 1.2 |
| **Urine** | 0- 24 h | 0.013 | 0.038 | 0.026 | 0.024 | 0.025 | 0.010 |
| | 24-48 h | < 0.003 | 0.015 | 0.003 | < 0.002 | 0.006 | 0.006 |
| | 48-72 h | < 0.004 | 0.004 | < 0.004 | 0.002 | 0.003 | - |
| | **Subtotal** | 0.020 | 0.057 | 0.033 | 0.028 | 0.034 | 0.016 |
| **Faeces** | 0-24 h | 66.95 | 73.74 | 73.06 | 79.72 | 73.37 | 5.22 |
| | 24-48 h | 12.24 | 8.91 | 10.29 | 1.38 | 8.21 | 4.75 |
| | 48-72 h | 3.39 | 0.16 | < 0.06 | 3.40 | 1.73 | 1.92 |
| | **Subtotal** | 82.59 | 82.81 | 83.41 | 84.50 | 83.33 | 0.88 |
| Cage wash | | < 0.01 | < 0.01 | < 0.01 | < 0.01 | < 0.01 | - |
| **Total excreted** | | 82.62 | 82.78 | 83.45 | 84.54 | 83.35 | 0.88 |
| | | | | | | | |
| **GI-tract (incl content** | | 0.063 | 0.003 | 0.006 | 0.003 | 0.019 | 0.030 |
| Tissue residues | | | | | | | |
| Excised * | | 0.008 | 0.009 | 0.005 | 0.010 | 0.008 | 0.002 |
| Organs | | 0.002 | 0.002 | 0.002 | 0.002 | 0.002 | 0.000 |
| Carcass | | 0.032 | 0.013 | 0.028 | 0.012 | 0.021 | 0.010 |
| **Total Retained** | | 0.042 | 0.024 | 0.035 | 0.024 | 0.031 | 0.009 |
| | | | | | | | |
| **Total Recovery** | | 82.73 | 82.90 | 83.49 | 84.57 | 83.42 | 0.83 |

* : Sum of blood and tissues (excluding organs)

Table A25 Recovery of antimony in excreta and tissues from male rats after a single oral dose of 1000 mg $Sb_2O_3$/kg BW (group D male).
Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 32 | 34 | 36 | 38 | Mean | SD |
| mg Sb/kg BW | | 881 | 856 | 844 | 879 | 865 | 18 |
| mg $Sb_2O_3$/kg BW | | 1054 | 1025 | 1010 | 1053 | 1036 | 22 |
| **Urine** | 0- 24 h | 0.0061 | 0.0061 | 0.0068 | 0.0073 | 0.0066 | 0.0006 |
| | 24-48 h | 0.0008 | 0.0016 | 0.0008 | 0.0003 | 0.0009 | 0.0005 |
| | 48-72 h | 0.0003 | 0.0010 | 0.0003 | 0.0003 | 0.0005 | 0.0004 |
| | **Subtotal** | 0.0071 | 0.0087 | 0.0080 | 0.0079 | 0.0079 | 0.0007 |
| **Faeces** | 0-24 h | 95.49 | 99.23 | 97.03 | 101.77 | 98.38 | 2.73 |
| | 24-48 h | 0.75 | 3.09 | 1.67 | 1.22 | 1.68 | 1.01 |
| | 48-72 h | < 0.01 | 0.03 | < 0.01 | 0.01 | 0.01 | - |
| | **Subtotal** | 96.25 | 102.34 | 98.71 | 103.00 | 100.07 | 3.17 |
| Cage wash | | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | - |
| **Total excreted** | | 96.26 | 102.34 | 98.71 | 103.01 | 100.08 | 3.17 |
| | | | | | | | |
| **GI-tract (incl content** | | 0.000 | 0.001 | 0.001 | 0.006 | 0.002 | 0.003 |
| Tissue residues | | | | | | | |
| Excised* | | 0.0088 | 0.0029 | 0.0035 | 0.0021 | 0.0043 | 0.0030 |
| Organs | | 0.0003 | 0.0003 | 0.0003 | 0.0003 | 0.0003 | 0.0000 |
| Carcass | | 0.0007 | 0.0009 | 0.0009 | 0.0043 | 0.0017 | 0.0017 |
| **Total Retained** | | 0.0098 | 0.0041 | 0.0047 | 0.0066 | 0.0063 | 0.0026 |
| | | | | | | | |
| **Total Recovery** | | 96.27 | 102.36 | 98.72 | 103.02 | 100.09 | 3.18 |

* : Sum of blood and tissues (excluding organs)

Table A26 Recovery of antimony in excreta and tissues from female rats after a single oral dose of 1000 mg $Sb_2O_3$/kg BW (group D female).
Expressed as % of the dose.

| Dose | | Animal number | | | | | |
|---|---|---|---|---|---|---|---|
| | | 31 | 33 | 35 | 37 | Mean | SD |
| mg Sb/kg BW | | 835 | 882 | 838 | 852 | 852 | 22 |
| mg $Sb_2O_3$/kg BW | | 999 | 1056 | 1003 | 1020 | 1020 | 26 |
| **Urine** | 0- 24 h | 0.0051 | 0.0055 | 0.0053 | 0.0085 | 0.0061 | 0.0016 |
| | 24-48 h | 0.0023 | 0.0009 | 0.0010 | 0.0009 | 0.0013 | 0.0007 |
| | 48-72 h | 0.0018 | < 0.0003 | < 0.0004 | < 0.0003 | 0.0007 | 0.0007 |
| | **Subtotal** | 0.0091 | 0.0067 | 0.0066 | 0.0096 | 0.0080 | 0.0016 |
| **Faeces** | 0-24 h | 94.68 | 90.38 | 84.91 | 93.37 | 90.83 | 4.34 |
| | 24-48 h | 1.47 | 8.40 | 13.96 | 7.50 | 7.83 | 5.11 |
| | 48-72 h | 0.01 | 0.10 | 0.10 | 0.14 | 0.09 | 0.05 |
| | **Subtotal** | 96.17 | 98.88 | 98.97 | 101.01 | 98.76 | 1.99 |
| Cage wash | | < 0.001 | < 0.001 | < 0.001 | < 0.001 | < 0.001 | - |
| **Total excreted** | | 96.18 | 98.83 | 98.97 | 101.02 | 98.76 | 1.99 |
| | | | | | | | |
| **GI-tract (incl content)** | | < 0.001 | 0.001 | 0.001 | 0.008 | 0.003 | 0.004 |
| Tissue residues | | | | | | | |
| Excised * | | 0.0016 | 0.0015 | 0.0029 | 0.0032 | 0.0023 | 0.0009 |
| Organs | | 0.0005 | 0.0004 | 0.0004 | 0.0004 | 0.0004 | 0.0000 |
| Carcass | | 0.0011 | 0.0013 | 0.0013 | 0.0057 | 0.0023 | 0.0022 |
| **Total Retained** | | 0.0031 | 0.0031 | 0.0046 | 0.0093 | 0.0050 | 0.0029 |
| | | | | | | | |
| **Total Recovery** | | 96.18 | 98.83 | 98.98 | 101.03 | 98.76 | 1.99 |

* : Sum of blood and tissues (excluding organs)

Table A27 Recovery of antimony in urine from male rats during a 14 days repeated oral dose of 1000 mg $Sb_2O_3$/kg BW and 3 days after (group E male).
Expressed as µg Sb excreted per day.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 52 | 54 | 56* | 58 | Mean | SD |
| Day | | | | | | |
| 1 | 26.6 | 24.4 | - | 40.4 | 30 | 9 |
| 2 | 18.6 | 17.3 | - | 39.2 | 25 | 12 |
| 3 | 39.0 | 21.8 | - | 33.3 | 31 | 9 |
| 4 | 31.3 | 25.3 | - | 30.7 | 29 | 3 |
| 5 | 26.8 | 11.9 | - | 46.8 | 28 | 18 |
| 6 | 30.3 | 21.9 | - | 33.4 | 29 | 6 |
| 7 | 23.2 | 17.4 | - | 53.4 | 31 | 19 |
| 8 | 23.4 | 17.5 | - | 29.0 | 23 | 6 |
| 9 | 22.7 | 15.4 | - | 28.3 | 22 | 6 |
| 10 | 19.7 | 14.5 | - | 26.6 | 20 | 6 |
| 11 | 14.1 | 19.5 | - | 22.8 | 19 | 4 |
| 12 | 18.5 | 17.3 | - | 21.3 | 19 | 2 |
| 13 | 20.7 | 20.4 | - | 20.9 | 21 | 0 |
| 14 | 20.2 | 15.9 | - | 19.4 | 18 | 2 |
| 15 | 4.2 | 7.0 | - | 5.2 | 5 | 1 |
| 16 | 3.7 | 2.3 | - | 2.5 | 3 | 1 |

* Animal died as a result of incorrect dosing at day 8.

Figure A2: Recovery of antimony in urine from male rats during a 14 days repeated oral dose of 1000 mg $Sb_2O_3$ /kg BW and 3 days after (group E male).
Expressed as µg Sb excreted per day.

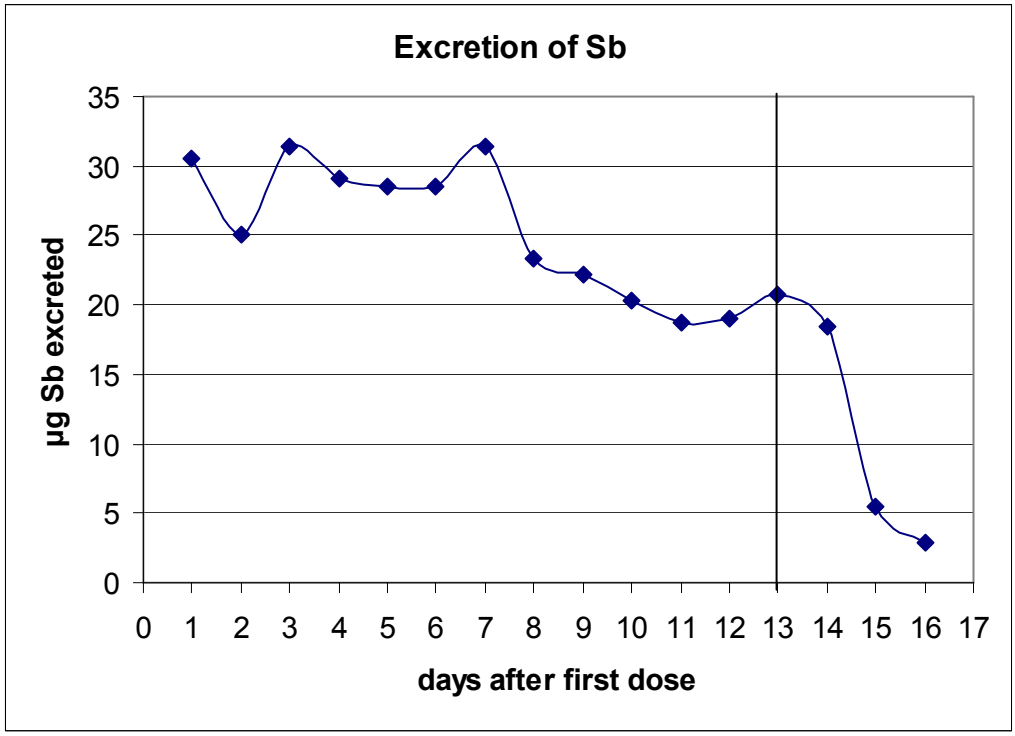
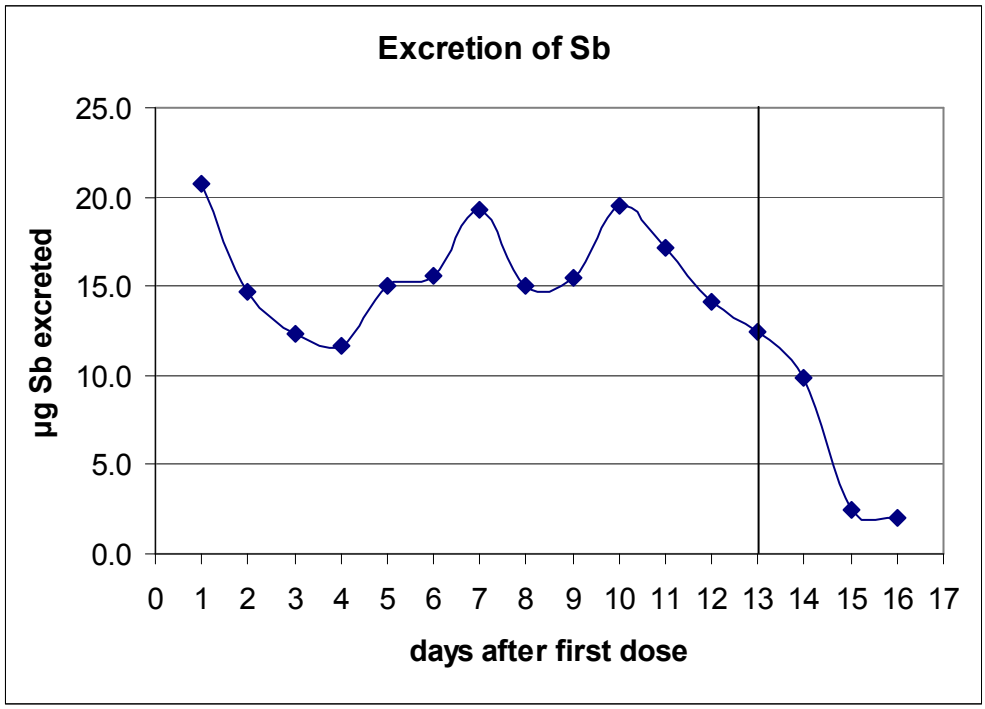


Table A28 Recovery of antimony in urine from female rats during a 14 days repeated oral dose of 1000 mg $Sb_2O_3$/kg BW and 3 days after (group E female.) Expressed as µg Sb excreted per day.

| | Animal number | | | | | |
|---|---|---|---|---|---|---|
| | 51 | 53 | 55 | 57 | Mean | SD |
| Day | | | | | | |
| 1 | 26.2 | 15.7 | 25.2 | 16.0 | 20.7 | 26.2 |
| 2 | 13.8 | 16.3 | 18.0 | 10.4 | 14.6 | 13.8 |
| 3 | 13.0 | 16.3 | 8.9 | 11.1 | 12.3 | 13.0 |
| 4 | 13.4 | 12.7 | 10.8 | 9.5 | 11.6 | 13.4 |
| 5 | 19.7 | 15.0 | 68.2* | 10.4 | 15.1 | 19.7 |
| 6 | 19.1 | 14.2 | 342* | 13.6 | 15.6 | 19.1 |
| 7 | 17.1 | 27.6 | 289* | 13.3 | 19.3 | 17.1 |
| 8 | 18.5 | 15.2 | 160* | 11.5 | 15.1 | 18.5 |
| 9 | 19.2 | 14.9 | 32* | 12.4 | 15.5 | 19.2 |
| 10 | 15.8 | 17.1 | 22.0 | 23.3 | 19.5 | 15.8 |
| 11 | 17.5 | 15.3 | 19.6 | 16.4 | 17.2 | 17.5 |
| 12 | 12.7 | 11.1 | 19.4 | 13.4 | 14.2 | 12.7 |
| 13 | 11.6 | 8.4 | 21.1 | 8.5 | 12.4 | 11.6 |
| 14 | 11.8 | 8.4 | 10.2 | 9.2 | 9.9 | 11.8 |
| 15 | 2.3 | 1.9 | 3.3 | 2.2 | 2.4 | 2.3 |
| 16 | 0.9 | 0.9 | 4.8 | 1.4 | 2.0 | 0.9 |

* Values not used for the calculation of the mean because the urine was contaminated with faeces

Figure A3: Recovery of antimony in urine from female rats during a 14 days repeated oral dose of 1000 mg $Sb_2O_3$/kg BW and 3 days after (group E female). Expressed as µg Sb excreted per day.



# Appendix 7 Tissue distribution of antimony – individual data

Table A29 Tissue distribution of antimony in male rats sacrificed 3 days after a single intravenous (IV) target dose of 1.57 mg $SbCl_3$/kg BW (group A). Expressed as ng Sb/g tissue.

| | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | 2 | 4 | 6 | 8 | Mean | SD | LOD |
| mg Sb/kg BW | 0.752 | 0.743 | 0.746 | 0.768 | 0.752 | 0.011 | - |
| mg $Sb_2O_3$/kg BW | 1.408 | 1.391 | 1.396 | 1.439 | 1.409 | 0.021 | - |
| Whole blood | 923 | 1325 | 1158 | 1039 | 1111 | 172 | 0.6 |
| Plasma | 2.9 | 2.8 | 2.8 | 3.6 | 3.1 | 0.4 | 0.6 |
| Bone marrow | 1114 | 1037 | 1283 | 897 | 1083 | 161 | 71 |
| Femurs | 282 | 206 | 183 | 184 | 214 | 47 | 1.7 |

Table A30 Tissue distribution of antimony in male rats sacrificed 3 days after a single intraperitoneal (IP) target dose of 100 mg $Sb_2O_3$/kg BW (group B). Expressed as ng Sb/g tissue.

| | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | 12 | 14 | 16 | 18 | Mean | SD | LOD |
| mg Sb/kg BW | 86.1 | 86.3 | 87.0 | 87.7 | 86.8 | 0.7 | - |
| mg $Sb_2O_3$/kg BW | 103.1 | 103.3 | 104.2 | 105.0 | 103.9 | 0.9 | - |
| Whole blood | 3884 | 2365 | 26505 | 12776 | 11383 | 11078 | 1 |
| Plasma | 23 | 13 | 26 | 11 | 18 | 7 | 1 |
| Bone marrow | 96284 | 21118 | 33204 | 11462 | 40517 | 38227 | 122 |
| Femurs | 15107 | 1872 | 7239 | 106 | 6081 | 6738 | 2 |

Table A31 Tissue distribution of antimony in male rats sacrificed 3 days after a single oral dose of 100 mg $Sb_2O_3$/kg BW (group C male).
Expressed as ng Sb/g tissue.

| | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | 22 | 24 | 26 | 28 | Mean | SD | LOD |
| mg Sb/kg BW | 87.7 | 81.7 | 91.7 | 88.2 | 87.3 | 4.2 | - |
| mg $Sb_2O_3$/kg BW | 104.9 | 97.8 | 109.8 | 105.6 | 104.6 | 5.0 | - |
| Whole blood | 171.2 | 172.2 | 54.4 | 324.9 | 180.7 | 110.9 | 0.6 |
| Plasma | 1.3 | 2.4 | 1.7 | 7.0 | 3.1 | 2.6 | 0.6 |
| Liver | 29.1 | 53.6 | 28.8 | 31.1 | 35.7 | 12.0 | 2.1 |
| Kidney | 14.5 | 19.4 | 15.9 | 8.9 | 14.7 | 4.4 | 1.2 |
| Lung | 27.6 | 42.7 | 28.1 | 42.6 | 35.3 | 8.6 | 1.8 |
| Heart | 17.5 | 31.8 | 21.4 | 17.4 | 22.0 | 6.8 | 2.4 |
| Spleen | 68.3 | 129.2 | 74.7 | 58.6 | 82.7 | 31.7 | 4.4 |
| Brain | 1.6 | 1.7 | 0.8 | 1.3 | 1.4 | 0.4 | 1.4 |
| Thyroid* | 155 | 149 | 131 | 195 | 158 | 27 | 74 |
| Testes | 3.4 | 2.6 | 1.7 | 1.6 | 2.3 | 0.8 | 0.9 |
| Prostate | 22.6 | 8.8 | 5.9 | 8.2 | 11.4 | 7.6 | 1.5 |
| Bone marrow* | 178 | 171 | 149 | 67 | 141 | 51 | 43 |
| Femur | 67.6 | 46.2 | 20.7 | 91.1 | 56.4 | 30.1 | 1.7 |
| Muscle | 6.8 | 5.2 | 53.6 | 6.7 | 18.1 | 23.7 | 1.5 |
| Skin | 78.4 | 53.4 | 24.3 | 8.5 | 41.2 | 31.0 | 2.4 |
| GI-tract including contents | 48.2 | 33.4 | 26.0 | 20.4 | 32.0 | 12.1 | 0.9 |
| Residual Carcass | 40.9 | 36.6 | 18.0 | 11.8 | 26.8 | 14.1 | 1.4 |

* These values were found for the tissues of group D male. The sample pretreatment for bioanalysis of bone marrow and thyroid was performed in a separate run than the one for all other organs and tissues, because these two organs have lower weights. Most likely during bioanalysis samples for these two tissues were switched with the samples of the D male group. This is corroborated with the results of the pilot study (V6379). The antimony concentration in bone marrow of animals dosed orally with 100 mg $Sb_2O_3$/kg BW was between 0.08-0.16 µg Sb/g (V6379), which is in line with a concentration found 0.07-0.18 µg Sb/g and not 0.69-1.31 µg Sb/g (see Table A33).

Table A32 Tissue distribution of Antimony in female rats sacrificed 3 days after a single oral dose of 100 mg $Sb_2O_3$/kg BW (group C female).
Expressed as ng Sb/g tissue.

| Dose | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 21 | 23 | 25 | 27 | Mean | SD | LOD |
| mg Sb/kg BW | 87.0 | 87.0 | 86.3 | 88.7 | 87.2 | 1.0 | - |
| mg $Sb_2O_3$/kg BW | 104.1 | 104.1 | 103.3 | 106.2 | 104.4 | 1.2 | - |
| Whole blood | 201.4 | 213.5 | 87.0 | 253.5 | 188.9 | 71.5 | 0.6 |
| Plasma | 2.5 | 6.8 | 0.8 | 2.8 | 3.2 | 2.5 | 0.6 |
| Liver | 26.7 | 23.2 | 19.8 | 29.8 | 24.9 | 4.3 | 3.1 |
| Kidney | 8.8 | 8.7 | 4.7 | 10.1 | 8.1 | 2.4 | 1.7 |
| Lung | 16.9 | 19.3 | 32.9 | 37.5 | 26.6 | 10.1 | 2.1 |
| Heart | 17.3 | 16.3 | 5.8 | 14.4 | 13.5 | 5.2 | 3.4 |
| Spleen | 67.4 | 41.3 | 29.3 | 60.2 | 49.6 | 17.4 | 5.6 |
| Brain | 1.0 | 1.0 | 0.7 | 1.6 | 1.1 | 0.4 | 1.5 |
| Thyroid* | 115 | 190 | 96 | 78 | 120 | 49 | 110 |
| Uterus* | 17.0 | 15.1 | 14.3 | 16.2 | 15.7 | 1.2 | 3.6 |
| Ovaries* | 18.6 | 31.9 | 35.3 | 31.9 | 29.4 | 7.4 | 18.8 |
| Bone marrow* | 113 | 49 | 97 | 98 | 89 | 28 | 76 |
| Femur | 20.5 | 21.2 | 62.7 | 48.0 | 38.1 | 20.8 | 2.2 |
| Muscle | 3.4 | 4.6 | 5.3 | 4.3 | 4.4 | 0.8 | 1.6 |
| Skin | 13.1 | 11.1 | 9.0 | 10.9 | 11.0 | 1.7 | 2.4 |
| GI-tract including contents | 551.8 | 29.2 | 45.9 | 25.7 | 163.2 | 259.3 | 1.4 |
| Residual Carcass | 36.7 | 15.8 | 18.6 | 14.2 | 21.3 | 10.4 | 1.6 |

* These values were found for the tissues of group D female. The sample pretreatment for bioanalysis of thyroid, uterus, ovaries and bone marrow was performed in a separate run than the one for all other organs and tissues, because these four organs have lower weights. Most likely during bioanalysis samples for these four tissues were switched with the samples of the D female group.

Table A33 Tissue distribution of antimony in male rats sacrificed 3 days after a single oral dose of 1000 mg $Sb_2O_3$/kg BW (group D male).
Expressed as ng Sb/g tissue.

| | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | 32 | 34 | 36 | 38 | Mean | SD | LOD |
| mg Sb/kg BW | 881 | 856 | 844 | 879 | 865 | 18 | - |
| mg $Sb_2O_3$/kg BW | 1054 | 1025 | 1010 | 1053 | 1036 | 22 | - |
| Whole blood | * | 718.3 | 864.6 | 539.5 | 707.5 | 162.8 | 0.6 |
| Plasma | 1.9 | 2.8 | 4.6 | 1.9 | 2.8 | 1.3 | 0.6 |
| Liver | 50.7 | 38.9 | 33.8 | 39.7 | 40.8 | 7.1 | 2.2 |
| Kidney | 7.7 | 14.7 | 14.1 | 11.5 | 12.0 | 3.2 | 1.3 |
| Lung | 48.6 | 42.6 | 42.8 | 29.1 | 40.8 | 8.3 | 1.6 |
| Heart | 44.8 | 45.6 | 42.8 | 33.8 | 41.8 | 5.4 | 2.6 |
| Spleen | 193.3 | 169.0 | 226.2 | 200.4 | 197.2 | 23.5 | 4.9 |
| Brain | 2.4 | 2.2 | 2.5 | 1.8 | 2.2 | 0.3 | 1.3 |
| Thyroid** | 1271 | 1558 | 1567 | 1632 | 1507 | 161 | 83 |
| Testes | 3.6 | 2.7 | 3.0 | 1.7 | 2.8 | 0.8 | 0.9 |
| Prostate | 8.9 | 7.3 | 8.8 | 8.9 | 8.5 | 0.8 | 1.4 |
| Bone marrow** | 1311 | 1958 | 804 | 694 | 1192 | 577 | 57 |
| Femur | 76.0 | 36.9 | 47.1 | 29.9 | 47.5 | 20.3 | 1.8 |
| Muscle | 4.1 | 3.1 | 6.2 | 6.5 | 5.0 | 1.6 | 1.1 |
| Skin | 12.0 | 12.5 | 13.6 | 0.2 | 9.6 | 6.3 | 1.8 |
| GI-tract including contents | 22.1 | 56.7 | 53.2 | 525.6 | 164.4 | 241.3 | 1.0 |
| Residual Carcass | 8.3 | 10.3 | 10.0 | 48.6 | 19.3 | 19.5 | 1.2 |

* a value of 2154 ngSb/g was found which was considered as an outlier or mistake in determination, value not use for calculation of mean and SD

** These values were found for the tissues of group C male. The sample pretreatment for bioanalysis of bone marrow and thyroid was performed in a separate run than the one for all other organs and tissues, because these two organs have lower weights. Most likely during bioanalysis samples for these two tissues were switched with the samples of the C male group. This is corroborated with the results of the pilot study (V6379).

Table A34 Tissue distribution of antimony in female rats sacrificed 3 days after a single oral dose of 1000 mg $Sb_2O_3$/kg BW (group D female).
Expressed as µg Sb/g tissue.

| | Animal number | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose | 31 | 33 | 35 | 37 | Mean | SD | LOD |
| mg Sb/kg BW | 835 | 882 | 838 | 852 | 852 | 22 | - |
| mg $Sb_2O_3$/kg BW | 999 | 1056 | 1003 | 1020 | 1020 | 26 | - |
| Whole blood | 481.0 | 600.9 | 652.4 | 823.5 | 639.5 | 142.2 | 0.6 |
| Plasma | 3.4 | 1.3 | 0.9 | 4.6 | 2.6 | 1.8 | 0.6 |
| Liver | 75.5 | 53.7 | 55.5 | 68.4 | 63.3 | 10.4 | 3.3 |
| Kidney | 18.9 | 21.6 | 20.8 | 28.6 | 22.5 | 4.2 | 1.7 |
| Lung | 30.1 | 72.4 | 63.8 | 77.2 | 60.9 | 21.2 | 2.3 |
| Heart | 35.3 | 36.3 | 39.5 | 52.4 | 40.9 | 7.9 | 3.5 |
| Spleen | 89.4 | 108.3 | 102.3 | 150.2 | 112.6 | 26.3 | 6.1 |
| Brain | 0.6 | 0.9 | 0.9 | 1.5 | 1.0 | 0.4 | 1.4 |
| Thyroid* | 2229 | 1191 | 2444 | 2547 | 2102 | 622 | 83 |
| Uterus* | 7.1 | 7.8 | 6.8 | 15.5 | 9.3 | 4.2 | 2.6 |
| Ovaries* | 500 | 203 | 228 | 118 | 262 | 166 | 16 |
| Bone marrow* | 2246 | 2831 | 1845 | 1061 | 1996 | 743 | 91 |
| Femur | 44.5 | 26.7 | 25.9 | 29.1 | 31.6 | 8.7 | 2.2 |
| Muscle | 6.1 | 2.9 | 3.7 | 5.9 | 4.7 | 1.6 | 1.3 |
| Skin | 19.7 | 17.0 | 11.8 | * | 16.2 | 4.0 | 2.3 |
| GI-tract including contents | 29.4 | 78.0 | 75.9 | 862.5 | 261.5 | 401.3 | 1.4 |
| Residual Carcass | 11.6 | 14.0 | 14.2 | 65.4 | 26.3 | 26.1 | 1.7 |

* These values were found for the tissues of group C female. The sample pretreatment for bioanalysis of thyroid, uterus, ovaries and bone marrow was performed in a separate run than the one for all other organs and tissues, because these four organs have lower weights. Most likely during bioanalysis samples for these four tissues were switched with the samples of the C female group.

Table A35 Tissue distribution of antimony in male rats sacrificed 3 days after a 14 days repeated oral dose of 1000 mg $Sb_2O_3$/kg BW (group E male).
Expressed as ng Sb/g tissue.

| | Animal Number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 52 | 54 | 56* | 58 | Mean | SD | LOD |
| Whole blood | 8135 | 7626 | ns | 9074 | 8278 | 735 | 0.6 |
| Plasma | 20 | 22 | ns | 21 | 21 | 1.1 | 0.6 |
| Liver | 672 | 870 | ns | 927 | 823 | 134 | 2.2 |
| Kidney | 303 | 279 | ns | 388 | 323 | 57 | 1.2 |
| Lung | 658 | 748 | ns | 833 | 746 | 88 | 1.7 |
| Heart | 763 | 352 | ns | 813 | 643 | 253 | 2.5 |
| Spleen | 1340 | 1330 | ns | 1786 | 1485 | 261 | 4.7 |
| Brain | 35 | 24 | ns | 30 | 30 | 5.6 | 1.3 |
| Thyroid* | 3177 | 2367 | ns | 2373 | 2639 | 466 | 83 |
| Testes | 44 | 33 | ns | 40 | 39 | 5.8 | 0.8 |
| Prostate | 72 | 76 | ns | 92 | 80 | 10.4 | 1 |
| Bone marrow* | 1946 | 2744 | ns | 2766 | 2486 | 467 | 98 |
| Femur | 274 | 182 | ns | 307 | 254 | 65 | 1.7 |
| Muscle | 53 | 29 | ns | 36 | 39 | 13 | 1.1 |
| Skin | 156 | 50 | ns | 64 | 90 | 58 | 2.0 |
| GI-tract including contents | 344 | 588 | ns | 498 | 477 | 124 | 1.0 |
| Residual Carcass | 559 | 151 | ns | 200 | 303 | 223 | 1.0 |

* Animal died as a result of incorrect dosing at day 8.
ns no sample

Table A36 Tissue distribution of Sb in female rats sacrificed 3 days after a 14 days repeated oral dose of 1000 mg $Sb_2O_3$/kg BW (group E female).
Expressed as ng Sb/g tissue.

| Dose | Animal Number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 51 | 53 | 55 | 57 | Mean | SD | LOD |
| Whole blood | 7552 | 7031 | 6744 | 6218 | 6886 | 557 | 0.6 |
| Plasma | 11 | 12 | 7 | 9 | 10 | 2 | 0.6 |
| Liver | 750 | 597 | 673 | 680 | 675 | 63 | 2.7 |
| Kidney | 194 | 264 | 337 | 248 | 261 | 59 | 1.5 |
| Lung | 927 | 958 | 909 | 735 | 882 | 100 | 2.1 |
| Heart | 447 | 413 | 222 | 344 | 356 | 99 | 3.1 |
| Spleen | 1224 | 1419 | 1322 | 1580 | 1386 | 152 | 5.5 |
| Brain | 21 | 16 | 18 | 15 | 17 | 3 | 1.4 |
| Thyroid | 2776 | 2227 | 2032 | 2067 | 2276 | 344 | 99 |
| Uterus | 114 | 81 | 165 | 105 | 116 | 35 | 2.9 |
| Ovaries | 736 | 707 | 630 | 585 | 665 | 69 | 14 |
| Bone marrow | 3293 | 5048 | 4158 | 1568 | 3517 | 1484 | 134 |
| Femur | 348 | 262 | 213 | 236 | 265 | 59 | 2.1 |
| Muscle | 36 | 51 | 47 | 42 | 44 | 7 | 1.0 |
| Skin | 79 | 110 | 134 | 90 | 103 | 24 | 1.8 |
| GI-tract including contents | 158 | 344 | 814 | 224 | 385 | 296 | 1.0 |
| Residual Carcass | 156 | 207 | 372 | 147 | 221 | 104 | 1.4 |

Table A37 Tissue distribution of antimony in control rats (group F male).
Expressed as ng Sb/g tissue.

| | Animal Number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 62 | 64 | 66 | 68 | Mean | SD | LOD |
| Whole blood | 3.0 | 2.6 | 2.8 | 2.7 | 2.8 | 0.2 | 0.6 |
| Plasma | 1.9 | 1.7 | 1.6 | 2.1 | 1.8 | 0.2 | 0.6 |
| Liver | 5.2 | 2.9 | 3.1 | 4.4 | 3.9 | 1.1 | 2.3 |
| Kidney | 2.9 | 2.2 | 2.7 | 2.9 | 2.7 | 0.4 | 1.3 |
| Lung | 4.7 | 3.4 | 2.3 | 4.0 | 3.6 | 1.0 | 1.7 |
| Heart | 3.7 | 4.2 | 3.4 | 3.1 | 3.6 | 0.5 | 2.5 |
| Spleen | 12.6 | 9.2 | 6.8 | 11.4 | 10.0 | 2.5 | 4.5 |
| Brain | 0.6 | 0.8 | 0.4 | 0.5 | 0.6 | 0.2 | 1.3 |
| Thyroid | 105 | 113 | 96 | 77 | 98 | 15 | 78 |
| Testes | 0.6 | 0.6 | 0.9 | 0.8 | 0.7 | 0.1 | 0.8 |
| Prostate | 7.8 | 12.3 | 7.3 | 10.5 | 9.5 | 2.4 | 1.8 |
| Bone marrow | 141 | 70 | 68 | 43 | 80 | 42 | 54 |
| Femur | 21.4 | 17.7 | 23.7 | 12.8 | 18.9 | 4.8 | 1.9 |
| Muscle | * | 4.4 | 6.9 | 1.6 | 2.7 | 1.4 | 1.4 |
| Skin | * | 3.1 | 5.2 | 0.7 | 2.3 | 1.8 | 1.8 |
| GI-tract including contents | 24.5 | 18.2 | 21.4 | 16.6 | 20.1 | 3.5 | 1.0 |
| Residual Carcass | 25.4 | 4.9 | 5.3 | 5.9 | 10.4 | 10.0 | 1.3 |

* sample lost during sample pretreatment bioanalysis

Table A38 Tissue distribution of antimony in control rats (group F female). Expressed as ng Sb/g tissue.

| | Animal Number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 61 | 63 | 65 | 67 | Mean | SD | LOD |
| Whole blood | 3.1 | 2.7 | 3.4 | 2.6 | 3.0 | 0.4 | 0.6 |
| Plasma | 3.1 | 3.5 | 2.3 | 2.4 | 2.8 | 0.6 | 0.6 |
| Liver | 2.7 | 3.6 | 3.1 | 2.5 | 3.0 | 0.5 | 3.1 |
| Kidney | 1.9 | 2.2 | 3.5 | 2.2 | 2.4 | 0.7 | 1.7 |
| Lung | 2.5 | 1.9 | 1.2 | 3.1 | 2.2 | 0.8 | 1.7 |
| Heart | 3.6 | 2.6 | 3.2 | 3.2 | 3.1 | 0.4 | 3.1 |
| Spleen | 90.9 | 13.2 | 15.2 | 8.5 | 32.0 | 39.4 | 6.2 |
| Brain | 1.5 | 0.5 | 0.4 | 0.5 | 0.7 | 0.5 | 1.4 |
| Thyroid | 124 | 412 | 96 | 147 | 195 | 146 | 97 |
| Uterus | 31.7 | 5.6 | 13.3 | 10.3 | 15.2 | 11.5 | 2.7 |
| Ovaries | 11.9 | 19.9 | 19.0 | 18.6 | 17.3 | 3.7 | 16.3 |
| Bone marrow | 214 | 116 | 108 | 131 | 142 | 49 | 185 |
| Femur | 6.6 | 10.9 | 10.8 | 11.5 | 10.0 | 2.3 | 2.2 |
| Muscle | 3.2 | 3.4 | 2.2 | 4.4 | 3.3 | 0.9 | 1.2 |
| Skin | 1.5 | 0.9 | 0.8 | 2.7 | 1.5 | 0.9 | 1.5 |
| GI-tract including contents | 18.9 | 17.5 | 11.8 | 14.4 | 15.6 | 3.2 | 1.6 |
| Residual Carcass | 8.5 | 5.3 | 5.0 | 4.2 | 5.7 | 1.9 | 1.7 |

# Appendix 8 Endorsement of Compliance

voedsel en waren autoriteit

## ENDORSEMENT OF COMPLIANCE

**WITH THE OECD PRINCIPLES OF**
**GOOD LABORATORY PRACTICE**

Pursuant to the Netherlands GLP Compliance Monitoring Programme and according to Directive 2004/9/EC the conformity with the OECD Principles of GLP was assessed on 7-11 June 2004 at

TNO Nutrition and Food Research
Utrechtseweg 48, P.O. Box 360
3700 AJ ZEIST

It is herewith confirmed that the afore-mentioned test facility is currently operating in compliance with the OECD Principles of Good Laboratory Practice in the following areas of expertise: Toxicity, mutagenicity, biodegradation, residues, analytical and clinical chemistry, kinetics and metabolism, and occupational toxicity.

The Hague, 19 August 2004

NEDERLAND STAATSTOEZICHT OP DE VOLKSGEZONDHEID

Dr Th. Helder
GLP Compliance Monitoring Department

Inspectorate for Health Protection and Veterinary Public Health
Food and Consumer Product Safety Authority